

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

PFIZER INC.,
Petitioner,

v.

NOVO NORDISK A/S,
Patent Owner.

Inter Partes Review No. IPR2020-01252

United States Patent No. 8,114,833

Issued: February 14, 2012

Filed: May 17, 2006

Title: Propylene Glycol-Containing Peptide Formulations Which Are Optimal for
Productions and for Use in Injection Devices

**EXPERT DECLARATION OF LAIRD FORREST, PH.D.
IN SUPPORT OF PETITION FOR *INTER PARTES* REVIEW**

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TABLE OF CONTENTS

	Page
1. QUALIFICATIONS AND BACKGROUND	6
A. Education and Experience; Prior Testimony	6
B. Bases for Opinions and Materials Considered.....	10
C. Scope of Work.....	10
2. SUMMARY OF OPINIONS.....	11
3. LEGAL STANDARDS	12
4. PERSON OF ORDINARY SKILL IN THE ART	14
5. THE '833 PATENT (EX. 1001).....	15
6. CLAIM CONSTRUCTION	19
7. BACKGROUND	19
A. GLP-1 Agonists, Including Liraglutide, Were Well Known in the Art.....	19
B. Parenteral Peptide Dosage Forms	20
C. Stability of Peptide Formulations and Selection of Excipients	30
i. Use of Propylene Glycol in Peptide Formulations	32
ii. Propylene Glycol is Safe.....	34
iii. Propylene Glycol's Advantages Over Other Isotonic Agents ..	34
8. SCOPE AND CONTENT OF THE PRIOR ART REFERENCES	38
A. Flink (Ex. 1004)	38
B. Betz (Ex. 1005)	48
C. Other Art That Informs the Person of Ordinary Skill's Knowledge ..	51
i. U.S. Patent No. 6,268,343 ("Knudsen I") (Ex. 1006)	51
ii. Eur. Patent. App. Pub. No. EP0923950 ("Ibaraki") (Ex. 1007)	51
iii. Powell (Ex. 1008)	52
iv. Epperson (Ex. 1009)	53
v. Jacobs (Ex. 1011).....	53

vi.	Int'l Patent Pub. No. WO 1999/040788 ("Young") (Ex. 1025)	54
vii.	Int'l Patent Pub. No. WO 03/072195 ("Khan") (Ex. 1014)	54
viii.	Int'l Patent Pub. NO. WO 95/022560 ("Dix") (Ex. 1019)	55
ix.	U.S. Patent No. 6,458,924 ("Knudsen II") (Ex. 1020)	56
x.	Int'l Patent Pub. NO. WO 00/037098 (Ex. 1021).....	56
xi.	Handbook of Pharmaceutical Excipients 2000, 2003 (Exs. 1022-1023)	57
xii.	Nail & Akers (Ex. 1024).....	57
xiii.	Bontempo (Ex. 1026).....	60
xiv.	Gatlin (Ex. 1027).....	61
xv.	Remington's 1990 (Ex. 1013).....	64
xvi.	Sturis (Ex. 1046)	66
xvii.	Chang (Ex. 1059)	66
xviii.	U.S. Patent No. 4,425,346 ("Horlington") (Ex. 1063)	67
xix.	U.S. Patent No. 6,207,684 ("Aberg") (Ex. 1064)	68
xx.	U.S. Patent No. 6,440,460 ("Gurny") (Ex. 1065).....	68
xxi.	Additional Prior Art References and Knowledge	69
9.	UNPATENTABILITY OF THE '833 PATENT	69
A.	Claims 1-15 of the '833 Patent Were Anticipated by or Would Have Been Obvious Over Flink	69
i.	Claim 1 Was Anticipated by or Would have Been Obvious Over Flink	69
1.	Flink disclosed the GLP-1 agonist	71
2.	Flink disclosed the claimed buffer	71
3.	Flink disclosed the claimed isotonic agent.....	74
4.	It would have been obvious to select propylene glycol..	74
5.	Calculating an appropriate concentration of propylene glycol was obvious	77
6.	Flink disclosed the claimed pH	80

ii.	Claims 2-4 Were Anticipated by or Would Have Been Obvious Over Flink.....	81
iii.	Claims 5-7 Were Anticipated by or Would Have Been Obvious Over Flink.....	81
iv.	Claims 8 and 9 Were Anticipated by or Would Have Been Obvious Over Flink.....	82
v.	Claim 10 Was Anticipated by or Would Have Been Obvious Over Flink	82
vi.	Claim 11 Was Anticipated by or Would Have Been Obvious Over Flink	83
vii.	Claim 12 Was Anticipated by or Would Have Been Obvious over Flink	84
viii.	Claim 13 Was Anticipated by or Would Have Been Obvious Over Flink	84
ix.	Claim 14 Was Anticipated by or Would Have Been Obvious Over Flink	85
x.	Claim 15 Was Anticipated by or Would Have Been Obvious Over Flink	86
B.	Claims 1-31 of the '833 Patent Would Have Been Obvious Over Flink in View of Betz.....	87
i.	Claims 1-15 Would Have Been Obvious Over Flink in View of Betz	87
1.	The common problem of peptide instability in formulations	90
2.	Flink taught that mannitol should not be used in formulations having a pH of 7.4.....	92
3.	It would have been obvious to solve the problem of precipitation with propylene glycol.....	93
ii.	Claim 16 Would Have Been Obvious Over Flink in View of Betz	95
iii.	Claims 17-19 Would Have Been Obvious Over Flink in View of Betz	97
iv.	Claims 20-22 Would Have Been Obvious Over Flink in View of Betz	97

v.	Claims 23, 26, and 29 Would Have Been Obvious Over Flink in View of Betz.....	98
vi.	Claims 24, 27, and 30 Would Have Been Obvious Over Flink in View of Betz.....	99
vii.	Claims 25, 28, and 31 Would Have Been Obvious Over Flink in View of Betz.....	101
10.	NO SECONDARY CONSIDERATONS OVERCOME <i>PRIMA FACIE</i> OBVIOUSNESS OF THE CLAIMED INVENTIONS	102
A.	The Methods Recited in the '833 Patent Produce No Unexpected Results	102
B.	There Was No Long-Felt But Unmet Need	103
C.	There Was No Industry Skepticism	104
D.	Copying By Generic Drug Makers Is Irrelevant.....	104
E.	A Blocking Patent Existed at the Time of the Claimed Invention ...	104

1. My name is Laird Forrest, Ph.D. I have been retained by counsel for Pfizer Inc. (“Pfizer”). I understand that Pfizer intends to petition for *inter partes* review (“IPR”) of U.S. Patent No. 8,114,833 (“the ’833 patent”), Ex. 1001, which is assigned to Novo Nordisk A/S. I also understand that, in the IPR petition, Pfizer will request that the United States Patent and Trademark Office cancel all claims of the ’833 patent as unpatentable. I submit this expert declaration to address and support Pfizer’s IPR petition for the ’833 patent.

1. QUALIFICATIONS AND BACKGROUND

A. Education and Experience; Prior Testimony

2. I am currently a Professor in the Department of Pharmaceutical Chemistry at the University of Kansas in Lawrence, Kansas, a position I have held since 2017. I am also Professor in the Bioengineering Center, a position I have held since 2011, and Professor in the Department of Medicinal Chemistry, a position I have held since 2015, both also at the University of Kansas. I have been a faculty at the University of Kansas since 2007.

3. I received a Bachelor of Science in Chemical Engineering from Auburn University in 1998, a Master of Science in Chemical Engineering from the University of Illinois in 2001, and a Ph.D. in Chemical and Biomolecular Engineering from the University of Illinois in 2003. I was a Postdoctoral Fellow in the Division of Pharmaceutical Sciences at the University of Wisconsin, Madison,

from 2004 to 2006. In 2006, I became Adjunct Assistant Professor in the Department of Pharmaceutical Sciences at Washington State University, a position I held until 2011. In 2007, I accepted a position as Assistant Professor in the Department of Pharmaceutical Chemistry at the University of Kansas. I was promoted to Associate Professor at the University of Kansas in 2013. I was then promoted to the rank of Professor in 2017.

4. Since 2009, I have been a Member of the Scientific and Medical Advisory Board of Exogenesis Corporation, which develops nanoscale surface modifications for implantable medical devices. I am the co-founder of HylaPharm LLC, founded in 2011, which specializes in reformulation of anti-cancer chemotherapeutics by modification of the delivery route and pharmacokinetics. Also, I am a co-founder of Hafion LLC, founded in 2016, which specializes in development of vaccines, and AeroByx LLC, founded in 2017, which specializes in the development of medications for treatment of neurological and metabolic disease. In addition, I am a co-founder of Vesarex, founded in 2018, which specializes in the development of ultrasound imaging devices and contrast agents. My research toward drug formulation has been competitively funded by multiple awards from the National Institutes of Health and the National Cancer Institute, the National Institute of Allergy and Infectious Disease, the American Cancer Society, the Department of

Defense, Susan G. Komen Race for the Cure, and the Pharmaceutical Research and Manufacturers of America Foundation (“PhRMA”), among others. In addition, I have been funded by the Food and Drug Administration (“FDA”) to develop methodologies for the in vitro determination of bioequivalence in follow-on complex botanical and biosimilar drug formulations.

5. I have received many awards and honors, including the Baxendale Innovation Award (2016), the University of Kansas Leading Light award (2014), the Japan Society for Promotion of Science Visiting Scholar Fellow (2010), the American Cancer Society Research Scholar (2008 to 2012), the American Association of Colleges of Pharmacy, New Investigators Award (2007), and the PhRMA Foundation Postdoctoral Fellow (2006), among others.

6. I am currently or have been in the past a member of various professional societies, including the American Association for Cancer Research, the American Association of Pharmaceutical Scientists, and the American Institute of Chemical Engineers. I serve or have served on numerous scientific review panels for the National Institutes of Health, the American Cancer Society, and the Association for International Cancer Research (United Kingdom). I am a standing member of the American Cancer Society review panel on Cancer Drug Development.

7. I have authored more than 90 peer-reviewed journal articles and 5 book chapters. I have also edited 2 special journal issues on drug delivery and a book on drug delivery and formulation.

8. I have taught drug formulation and biopharmaceutics, including all aspects of drug excipient choice and the effects of excipient modification on drug pharmacokinetics, ionic equilibrium, drug chemical stability, drug dissolution, and drug absorption, to clinical pharmacy students and graduate students studying pharmaceutical sciences since 2007.

9. I have experience in all aspects of parenteral, topical, and oral drug formulation and pharmacokinetics through my research and teaching. Additionally, as part of my work with HylaPharm, Exogenesis Inc., Atrin Pharmaceuticals, and Akari Therapeutics Inc., I have worked on pharmaceutical formulations for intramuscular, subcutaneous, intravenous, topical, and oral formulation.

10. In the past six years, I have testified in the following litigations:

- *Merck Sharp & Dohme Corp. v. Savior Lifetec Corp.*, No. 5:15-cv-00415-TWB (E.D.N.C.);
- *Medac Pharma, Inc. et al. v. Antares Pharma Inc. et al.*, No. 1:14-cv-01498-JBS-KMW (D.N.J.);
- *Halozyme, Inc. v. Joseph Matal (on behalf of USPTO)*, No. 1:16-cv-1580 (E.D. Va.);

- *Bracco Diagnostics v. Maia Pharm., Inc.*, No. 3:17-cv-13151 (D.N.J.);
- *Horizon Medicines LLC v. Dr. Reddy's Labs. Inc.*, No. 2:15-cv-03324-SRC-CLW (D.N.J.) (consolidated); and
- *Cydex Pharmaceuticals, Inc., v. Alembic Global Holding SA, Alembic Pharmaceuticals, Ltd., and Alembic Pharmaceuticals, Inc.*, No. 1:19-CV-00956-LPS (D.N.J.)

11. My *curriculum vitae*, which describes my experience and background in more detail, is attached as Exhibit A.

B. Bases for Opinions and Materials Considered

12. Exhibit B includes a list of the materials I considered, in addition to my experience, education, and training, in providing the opinions contained in this declaration.

C. Scope of Work

13. I have been retained by Pfizer as a technical expert to provide various opinions regarding the '833 patent. I am being compensated for my time at my standard consulting rate of \$600/hour. Neither the amount of my compensation nor the fact that I am being compensated has altered the opinions that I have given in this Declaration. My compensation is in no way dependent on the outcome of this proceeding. I do not have any current or past affiliation with Novo Nordisk A/S, or any of its affiliates presently known to me, or the named inventors on the '833 patent.

2. SUMMARY OF OPINIONS

14. In my view, claims 1-15 of the '833 patent were anticipated by International Patent Publication No. WO 2003/0002136 to Flink et al. ("Flink") (Ex. 1004), as described in detail below. Flink's claim 14 disclosed, in the context of the specification, each element of the inventions claimed in claims 1-15 of the '833 patent.

15. Also, claims 1-15 of the '833 patent would have been obvious over Flink, as described in detail below. In short, to the extent Flink would have been viewed as not anticipating the inventions claimed in the '833 patent, the inventions would have been obvious to a person of ordinary skill in the art because the POSA would have been motivated to combine the claimed elements with a reasonable expectation of success.

16. Additionally, claims 1-31 of the '833 patent would have been obvious over Flink in view of International Patent Publication No. WO 2004/0004781 to Betz and Stevens ("Betz") (Ex. 1005), as described in detail below. To the extent Flink would have been viewed as neither anticipating nor rendering obvious the claims of the '833 patent, a POSA would have understood from Betz to use propylene glycol in the GLP-1 formulation disclosed in Flink, with a reasonable expectation of success.

17. Finally, there are no apparent secondary considerations supporting nonobviousness of the claims. There is no evidence of unexpected results in view of the prior art, which also satisfied any need for the claimed invention. Further, there is no evidence of industry skepticism of the claimed invention, and any allegation that the invention is nonobvious because it was copied does not weight in this context. Finally, a blocking patent existed at the time of the claimed invention, which would have dissuaded anyone from developing the claimed formulations and methods, and reduces the weight to be given to any secondary considerations asserted in favor of patentability. I reserve the right to address any secondary considerations put forth by Patent Owner in any later response to this declaration or the petition it accompanies.

3. LEGAL STANDARDS

18. In preparing and forming my opinions set forth in this report, counsel has informed me regarding the relevant legal principles.

19. Counsel informed me that Pfizer bears the burden of proving unpatentability by a preponderance of the evidence. Counsel informed that this “preponderance of the evidence” standard means that Pfizer must show that unpatentability is more probable than not. I have taken these principles into account when forming my opinions in this case.

20. I have also been told that claims should be given their plain and ordinary meaning in light of the specification from the perspective of a person of ordinary skill in the art.

21. Counsel informed me that the question of whether the claims of a patent are anticipated by, or obvious in view of, the prior art is to be considered from the perspective of the person of ordinary skill in the art (“POSA”). Counsel further informed me that the answer to this question is determined as of the time the invention was made. I understand from counsel that the concept of patent obviousness involves four factual inquiries: (1) the scope and content of the prior art; (2) the differences between the claimed invention and the scope and content of the prior art; (3) the level of ordinary skill in the art; and (4) whether there are additional factors present that may argue against a conclusion of obviousness (i.e., “secondary considerations”) such as unexpected results attributable to the invention, or whether the invention met a long-felt but unmet need.

22. Counsel informed me that an invention may be found obvious when there is some recognized reason to solve a problem, and there are a finite number of identified, predictable, and known solutions, and a person of ordinary skill in the art has good reason to pursue the known options within his or her technical grasp. If such an approach leads to the expected success, it is likely not the product of innovation but of ordinary skill and common sense. In such a circumstance, when a

patent simply arranges old elements with each performing its known function and yields no more than what one would expect from such an arrangement, the combination is obvious.

23. Counsel informed me that a prior art reference anticipates a claimed invention if the prior art reference disclosed each of the claimed elements of the invention either expressly or inherently. A claim element is inherent in the anticipating reference if that element, or characteristic, is the natural result that flows from the reference's explicit limitations. In this regard, counsel informed me that a reference can anticipate a claim even if the reference does not expressly spell out all the limitations arranged or combined as in the claim, if a person of skill in the art, reading the reference, would at once envisage the claimed arrangement or combination. Counsel has informed me that if a patent claims a composition in terms of a function, property, or characteristic, and the composition itself is in the prior art, then the claim may be anticipated or obvious in view of the prior art reference disclosing the composition.

4. PERSON OF ORDINARY SKILL IN THE ART

24. I have been informed by counsel that the obviousness analysis is to be conducted from the perspective of a person of ordinary skill in the art (a "person of ordinary skill" or "skilled artisan") at the time of the invention.

25. I have also been informed by counsel that in defining a person of ordinary skill the following factors may be considered: (1) the educational level of the inventor; (2) the type of problems encountered in the art; (3) prior art solutions to those problems; (4) rapidity with which innovations are made; and (5) sophistication of the technology and educational level of active workers in the field.

26. Thus, in this report, unless stated otherwise, I opine from the perspective of the person of ordinary skill in the art at the time of the invention (POSA). The POSA is (1) a Pharm. D., or a Ph.D. in pharmacy, chemical engineering, bioengineering, chemistry, or related discipline; with (2) at least two years of experience in the area of protein or peptide therapeutic development and/or manufacturing; and (3) experience with the development, design, manufacture, or formulation of therapeutic agents, and the literature concerning protein or peptide formulation and design.

27. For purposes of this declaration, my opinion is based on the knowledge or understanding of a POSA as of the earliest possible priority date claimed on the cover of the '833 patent, November 20, 2003 (see below, ¶30), unless specified otherwise.

5. THE '833 PATENT (EX. 1001)

28. I have read the '833 patent, entitled "Propylene glycol-containing peptide formulations which are optimal for production and for use in injection

devices.” According to its cover page, the ’833 patent was filed on May 17, 2006 as U.S. Patent Application No. 11/435,977, a continuation application of No. PCT/DK2004/000792, filed on November 18, 2004. U.S. Patent Application No. 11/435,977 also claims priority to U.S. Provisional Application No. 60/524,653, filed on November 24, 2003, as well as a Danish application filed November 20, 2003.

29. I understand that Pfizer is challenging claims 1-31 of the ’833 patent as unpatentable. The ’833 patent includes five independent claims: claims 1, 16, 23, 26, and 29.

30. Independent claim 1 recites:

1. A pharmaceutical formulation comprising at least one GLP-1 agonist, a disodium phosphate dihydrate buffer and propylene glycol, wherein said propylene glycol is present in said formulation in a final concentration of from about 1 mg/ml to about 100 mg/ml and wherein said formulation has a pH of from about 7.0 to about 10.0.

31. Dependent claims 2-15 depend from claim 1. Dependent claims 2-4 relate to the concentration of propylene glycol in the formulation. Dependent claims 5-7 relate to the pH of the formulation. Dependent claims 8-9 recite that the formulation contains a preservative, and identifies its concentration, respectively. Dependent claims 10-15 relate to the identity of the GLP-1 agonist.

32. Independent claim 16 recites:

16. A method of preparing a GLP-1 agonist formulation suitable for use in an injection device, said method comprising preparing a formulation containing a GLP-1 agonist, propylene glycol, a disodium phosphate dihydrate buffer, and a preservative, wherein said propylene glycol is present in a concentration from about 1 mg/ml to about 100 mg/ml, and wherein said formulation has a pH from about 7.0 to about 10.0, and wherein said GLP-1 agonist, said propylene glycol and said buffer and preservative are mixed together to produce said formulation as follows:

- a) preparing a first solution by dissolving preservative, propylene glycol and buffer in water;
- b) preparing a second solution by dissolving the GLP-1 agonist in water;
- c) mixing the first and second solutions; and adjusting the pH of the mixture in c) to a pH of from about 7.0 to about 10.0.

33. Dependent claims 17-22 depend from claim 16. Dependent claims 17-19 relate to the concentration of propylene glycol in the formulation. Dependent claims 20-22 relate to the pH of the formulation.

34. Independent claim 23 recites:

23. A method for reducing deposits on production equipment during production of a GLP-1 agonist formulation, said method comprising replacing the isotonicity agent previously utilized in said formulation with propylene glycol at a concentration of between 1-100 mg/ml, and wherein said GLP-1 agonist formulation comprises a disodium phosphate dihydrate buffer.

35. Dependent claims 24 and 25 depend from claim 23. Dependent claim 24 recites that the reduction in deposits is measured by a simulated filling

experiment. Dependent claim 25 recites the group of isotonicity agents that could be replaced.

36. Independent claim 26 recites:

26. A method for reducing deposits in the final product during production of a GLP-1 agonist formulation, said method comprising replacing the isotonicity agent previously utilized in said formulation with propylene glycol at a concentration of between 1-100 mg/ml, and wherein said GLP-1 agonist formulation comprises a disodium phosphate dihydrate buffer.

37. Dependent claims 27 and 28 depend from claim 26. Dependent claim 27 recites that the reduction in deposits is measured by the number of vials and/or cartridges that must be discarded due to deposits. Dependent claim 28 recites the group of isotonicity agents that could be replaced.

38. Independent claim 29 recites:

29. A method for reducing the clogging of injection devices by a GLP-1 agonist formulation, said method comprising replacing the isotonicity agent previously utilized in said formulation with propylene glycol at a concentration of between 1-100 mg/ml, and wherein said GLP-1 agonist formulation comprises a disodium phosphate dihydrate buffer.

39. Dependent claims 30 and 31 depend from claim 29. Dependent claim 30 recites that the reduction in clogging is measured by a simulated in use study. Dependent claim 31 recites the group of isotonicity agents that could be replaced.

6. CLAIM CONSTRUCTION

40. I understand that the claim terms used in the '833 patent are to be understood according to their ordinary and customary meaning in light of the specification of the patent in which they appear. I further understand that Petitioner is not seeking to construe differently any terms in the claims of the '833 patent, although Petitioner does argue that the preambles of certain claims should be construed as not limiting the scopes of those claims.

7. BACKGROUND

A. GLP-1 Agonists, Including Liraglutide, Were Well Known in the Art

41. Human GLP-1 is a 37-amino acid peptide hormone ("GLP-1(1-37)") originating from proglucagon. Processing of proglucagon, yields two shorter forms of GLP-1: GLP-1(7-36)amide and GLP-1(1-37). Ex. 1006, 4:17-24. GLP-1(7-36) and GLP-1(1-37) have the following sequence:

His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-
 Leu- Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-
 Leu-Val-Lys- Gly-Arg-X

where X is H₂ for GLP-1(7-36) and X is Gly for GLP-1(1-37). Ex. 1006, 4:50-60.

42. By the priority date, GLP-1 agonists were well known in the art. The '833 patent itself identifies numerous disclosures of prior art GLP-1 agonists. *See* Ex. 1001, 4:38-52 (citing WO93/19175, WO99/43705, WO 99/43706,

WO99/43707, WO98/08871, WO02/46227, WO99/43708, WO99/43341, WO87/06941, WO90/11296, WO91/11457, WO98/43658, EP0708179, EP0699686, and WO01/98331) (Exs. 1031-1045, respectively); *see also* Ex. 1006 (U.S. Patent No. 6,268,343) at 268:15-16 (claim 23) (claiming liraglutide).

B. Parenteral Peptide Dosage Forms

43. Parenteral dosage forms are medicinal preparations that are intended to be given by injection into subcutaneous or muscular tissues, veins or arteries, joints, the spinal canal and other routes that are *para enteron* (Greek for “beside the intestine”). Ex. 1013 at 157-58, 354. In contrast, non-parenteral formulations are designed to be taken orally, topically, vaginally, via the rectum, and generally routes that require the medicament to pass through protective mucosal membranes. Ex 1013 at 157-58, 203, 354.

44. A POSA would understand that parenteral dosage forms have advantages in treating a patient for certain circumstances and conditions. Ex. 1013 at 157-58. For example, oral drugs pass through the stomach and into the intestines before they are absorbed into the blood, a process that can delay the time at which therapeutic levels in the blood are reached by as long as several hours. Ex. 1013 at 157-60; Ex. 1012 at 29-39. In contrast, the POSA would know that parenteral dosage forms are designed for more rapid distribution throughout the body, and consequently, earlier onset of pharmacological and therapeutic effects. Ex. 1013 at

157-58; Ex. 1012 at 109-11, 247-48. In the case of subcutaneous and intramuscular routes, the onset of action is not as rapid as intravenous delivery, but generally these routes still avoid many of the disadvantages of the oral administration. Ex. 1013 at 158; Ex. 1012 at 110-12, 248-50. In addition, the POSA would also know that parenteral dosages avoid “first-pass” metabolism—the hepatic metabolism and clearance of drug molecules from the portal venous blood (i.e. blood from gastro intestinal tract, gall bladder, pancreas and spleen)—which can limit systemic exposure to the drug and precludes the development of some drugs as oral medicaments. Ex. 1013 at 157, 177-78, 200-01; Ex. 1012 at 41-44, 109-14, 126.

45. The POSA would have also known that parenteral dosage forms offer similar advantages for peptide-based drugs. Ex. 1053 (Zhou) at 8. Like proteins, peptide-based drugs are composed of amino acids, which are broken down by gastric acid and proteolytic enzymes in the gastrointestinal tract when ingested orally, resulting in the drug being absorbed with other nutrients, eliminating their therapeutic activity. *Id.* at 2, 8; Ex. 1013 at 296-303. The POSA would recognize that delivering a protein or peptide-based drug by parenteral administration would maximize the amount of drug that reaches the blood, and that intravenous or subcutaneous administration is required for many peptide-based drugs. Ex. 1053 at 8; Ex. 1055 (Edwards) at 1. And although intravenous formulations ensure all of a peptide-based drug reaches the systemic circulation, poor disposition profiles may

lead to sub-optimum therapeutic benefits without frequent dosing. Ex. 1053 at 8. The POSA would have known that subcutaneous injection confers prolonged absorption that would extend the systemic exposure of drugs that are normally cleared rapidly, and may thereby increase the duration of therapeutic effect for certain drugs. Ex. 1013 at 158-59; Ex. 1052 (Schade) at 1, 3.

46. Certain parenteral formulations are no less convenient than oral administration. Intravenous formulations, require specialized training to prepare immediately before use and careful preparation and control of the infusion set and infusion solution. Ex. 1013 at 379-87. In contrast, patients can be trained to self-administer subcutaneous formulations, and patients usually prefer subcutaneous medications over intravenous infusions. Ex. 1051 (Robinson) at 1-2.

47. Despite the numerous advantages that parenteral dosage routes have, the POSA would have understood that certain physiological limitations and risks related to parenteral formulations must be carefully considered during their development, manufacturing and preparation. Ex. 1013 at 354-60, 376-77; Ex. 1012 at 283-85. For example, a POSA would have known that there were (and remain) “two potential disadvantages that are typically associated with parenteral therapy...tissue damage and injection pain.” Ex. 1027 at 13. There are two parameters related to a parenteral formulation that are “usually associated with tissue damage and injection pain,” pH and tonicity, and adjusting those parameters “can

minimize adverse effects.” *Id.* In addition, parenteral dosage forms are vulnerable to microbial infection whether injected through the skin or into an intravenous line because that route bypasses the protective skin and mucosal membranes that are in place to resist the entry of infectious agents and limit the absorption of environmental toxins. Ex. 1013 at 354, 390-91; Ex. 1012 at 187-88, 197. Hence, parenteral formulations must be manufactured and prepared under highly controlled and aseptic conditions. Ex. 1013 at 355, 362-64.

48. Even further, a dosage form is intended as multiple use (e.g., provided in a vial containing sufficient drug for multiple treatments), should include anti-microbial excipients or additives in the formulation. Ex. 1013 at 359. Moreover, the risks associated with receiving a formulation with impurities, infectious agents, or degraded ingredients are higher in parenteral formulations because once a parenteral formulation is administered, it cannot be readily removed from the system should a patient experience an adverse event or be improperly dosed. In contrast, oral drugs still in the stomach can be expelled using an emetic or gastric lavage. Ex. 1013 at 354-56, 278; Ex. 1012 at 247-50. To minimize the risks, a POSA would recognize that a parenteral must be designed so that the physical and chemical integrity of the drug formulation is maintained throughout manufacturing, storage and handling. Ex. 1013 at 157-59, 354-55, 362-64.

49. The POSA would have known of several factors important to the performance and safety of parenteral drug formulations. Ex. 1013 at 355-56. These factors include: pH, buffering capacity, avoiding particulates, biocompatibility of the vehicle, osmolarity, sterility, and choice of excipients. Ex. 1013 at 54-55, 358-59, 376-77; Ex. 1012 at 283-85; Ex. 1024 at 29-42.

50. pH and buffering capacity. A buffering system contains a weak acid and its conjugate base or a weak base and its conjugate acid. Ex. 1028 at 3-4. A buffer is “[a] solution that resists change in pH when an acid or alkali is added or when the solution is diluted.” *Id.* In other words, buffers “establish[] and maintain[] the product pH.” Ex. 1027 at 20. The use of a buffer is particularly important in parenteral formulations because they are designed to be injected directly into a patient, and product stability must be maintained. Ex. 1012 at 262, 279.

51. Generally, a POSA would design parenteral formulations to have a narrow range of pHs, i.e., the acidity or alkalinity would be contained within a small window, as the pH profile is generally the most important part of liquid formulation compatibility. Ex. 1013 at 54-55; Ex. 1012 at 146-51, 180. The venous blood has a normal pH range of 7.36 to 7.40, cells have an interior pH of 7.0 to 7.4, subcutaneous tissue has a pH of about 7.3 to 7.6, and most tissues are similarly near neutral pH (i.e. about 7.2 to 7.6), depending on the organ, disease, and other physiological

factors. Ex. 1048 (Gerwerk) at 2; Ex. 1013 at 128; Ex. 1049 (Madshus) at 1; Ex. 1057 (Martins 1995) at 30.

52. Ideally, a parenteral formulation should be “as close to physiological pH (7.4) as possible in order to minimize potential irritation upon injection,” but a wider pH range (e.g., between 5 and 9) is acceptable depending on the method of administration and the solubility of the drug. Ex. 1024, 4, 16-17; Ex. 1060, 1-2, 4-5; Ex. 1012 at 283-285.

53. Tissues may be injured by injection of solutions that are extremely acidic or alkaline. Ex. 1056 (Akiyama) at 1-3; Ex. 1054 (Napaporn) at 4, 6-8. And at extreme pH values of 2.3 and 11, cells are killed on contact. Ex. 1060 (Stranz) at 1; Ex. 1012 at 283-85. Thus, a POSA would have appreciated that a parenteral formulation should have a pH that is safe for the intended injection site and the intended volume. Ex. 1047 (Fransson) at 1, 3-4.

54. The POSA would have also understood that the stability and solubility of the drug product may be dependent on the formulation pH, and the final formulation pH must be designed considering both the stability and solubility of the drug balanced with the safety of the patient. Ex. 1047 at 1; Ex. 1013 at 54-55; Ex. 1012 at 146-52; Ex. 1024 at 16-21. Buffers in parenteral formulations are used to maintain the targeted pH until the drug is administered to maintain the chemical and

physical stability of the formulation during its intended shelf life. Ex. 1057 at 33; Ex. 1013 at 54-55; Ex. 1012 at 152.

55. The POSA would also have known that a parenteral formulation should be designed to have the minimum buffering capacity necessary to stabilize the drug because a buffering capacity that is too large could disrupt the buffering systems present in the body—especially if the formulation has a pH outside the normal physiological range. Ex. 1057 at 31-32; Ex. 1013 at 359; Ex. 1047 at 1, 3. In addition, buffer salts can affect the drug’s stability, in some instances directly reacting with and degrading the drug. Ex. 1012 at 152; Ex. 1058 (Borchert) at 26. Furthermore, it is likely that increasing the buffer capacity “will significantly increase ionic strength, which, in turn, may cause increase in frequency of pain upon injection due to the increased osmolality.” Ex. 1024, 20.

56. Avoidance of particulates. Particulates are insoluble matter in formulations or formulation containers, or excipient or drug components that have come out of solution due to, for example, degradation, chemical reactions, interactions with the container, temperature extremes, or limited solubility. Ex. 1058, 24-26; Ex. 1009. While some formulations useful for subcutaneous or intramuscular delivery may be purposely designed to have particulates, e.g., injectable suspensions, for many formulations, a POSA would know that particles are undesirable, and their generation must be minimized during manufacture and

preparation of the dosage form. Ex. 1058 at 1-3; Ex 1013 at 376; Ex. 1012 at 264-66. The unintended introduction of particulates into a parenteral formulation could lead to loss of drug activity, irritation at the injection site, immunological sensitization to the medicant and/or the excipients, anaphylactic shock, and/or cause an embolism or vessel blockage. *See* Ex. 1058 at 2 (general concern to prevent introduction of particulates); Ex 1067 at 8, Ex. 1013 at 376-77.

57. *Vehicles and diluents.* A POSA developing a parenteral formulation would have known that vehicles and/or diluents are necessary for most drug formulations and parenteral delivery routes. Ex. 1013 at 234, 356-58. The vehicle in parenteral formulations provides a liquid carrier for the drug. The vehicle may be composed of solvents, such as water; organic liquids (like propylene glycol, glycerin, ethanol or sesame oil); or combinations of those ingredients. Ex. 1013 at 358. When possible, water-based vehicles are often preferred due to the high solubility of polar drugs in water and the safety of aqueous vehicles. Ex. 1013 at 27-28, 235-38, 358; Ex. 1057 at 44-45; Ex. 1012 at 263. However, a POSA would have known that water alone is insufficient for the formulation of some parenteral drugs because drug molecules may be non-polar and have insufficient solubility in water, in which case an organic co-solvent may be used with the water to lower the vehicle polarity and increase drug solubility. Ex. 1013 at 27-29; Ex. 1057 at 65.

58. The POSA would have appreciated that several organic solvents have been used in FDA-approved drug formulations to improve solubility, and common texts such as Martin's Physical Pharmacy and Remington's Pharmaceutical Sciences provided guidance on the use of non-aqueous solvents in parenteral formulations. Ex. 1013 at 235-51, 354-60; Ex. 1057 at 43-68.

59. Tonicity and osmolarity. Osmolarity is a measure of the number of dissolved particles in a solution. Ex. 1013 at 305; Ex. 1057 at 16-19. In an aqueous solution, everything that is not water contributes to its osmolarity and osmolality. Ex. 1013 at 31-32, 305-06. For example, components such as electrolytes, nutrients, proteins, and other small and macro-molecules, all contribute to the osmolarity. *Id.* Further, osmolarity is a colligative property—meaning it is dependent on the number of solute molecules dissolved in solution irrespective of what those solute molecules are, i.e., all solutions with the same molar concentration of solute have the same osmolarity, irrespective of the solute. Ex. 1013 at 304-05; Ex. 1057 at 16-17.

60. Osmolality and osmolarity are different terms that describe the osmotic properties of solutions; the difference being that osmolality is the osmol of solute per kg of water and osmolarity is the osmol of solute per liter of solution. Ex. 1013 at 305-06. Osmolarity and osmolality are different quantities and may differ significantly for a given solution, but the terms are often used interchangeably because the values typically differ by less than 1% for most dilute biological

solutions and many dilute drug formulations. Ex. 1013 at 306. Physiological fluids such as blood and lacrimal fluid have an osmolarity of approximately 275-295 mOsmol/L, and normal values of most fluids likely fall within an even narrower range of 286 ± 4 mOsmol/kg, expressed as osmolality. Ex. 1013 at 306; Ex. 1057 at 19. A POSA would have known that a solution of 0.9% w/v sodium chloride is generally described as isosmotic with most physiological fluids, meaning that they have a similar number of dissolved particles per liter of solution. Ex. 1013 at 306. More generally, blood and 0.9% saline are also called isotonic; the term isotonic and the concept of tonicity are further described *infra* at ¶61. *Id.* If a solution has an osmolarity greater than 0.9% sodium chloride solution, the solution is hypertonic; if the osmolarity is less than 0.9% sodium chloride solution, the solution is hypotonic. Ex. 1013, 305-06. Hypertonic and hypotonic formulations can cause pain and irritation at the site of administration or undesirable complications (e.g., hemolysis, cellular dehydration). Ex. 1026 (Bontempo) at 117; Ex. 1013, 308. It is therefore desirable for a formulation that is delivered parenterally—especially when it is an injection—to be “isotonic” with body fluids. *Id.*; *see also* Ex. 1012 at 262.

61. A solution is isotonic with a given physiological fluid when there is no net gain or loss of water when cells contact the solution. Not all isosmotic solutions are also isotonic. For example, if a solute can freely diffuse through the membranes of red blood cells (RBCs), the osmolarity will rise within in the RBCs causing the

swelling and possible rupture. *Id.* at 305. Texts such as Remington's 1990 offer detailed instructions and tables for formulating pharmaceutical compositions that are isosmotic and/or isotonic with physiological fluids. Ex. 1013 at 305-21.

62. The POSA would have appreciated that a formulation may need to be isotonic with the intended injection space, i.e., the blood or subcutaneous tissue, to minimize the risk of hemolysis, tissue damage, and to minimize patient discomfort. Ex. 1013 at 32, 308; Ex. 1054 at 4-8; Ex. 1012 at 262. The POSA would know that parenteral formulations intended for intravenous use "can tolerate fairly wide ranges of 'tonicity' (osmolality or osmolarity) ... whereas subcutaneous or intramuscular routes may require tighter control of product tonicity." Ex. 1024, 4.

C. Stability of Peptide Formulations and Selection of Excipients

63. Ensuring that protein and peptide formulations remain stable in aqueous solutions is an important aspect of formulation development. *See, e.g.*, Ex. 1024, 4-5. Environmental factors a protein or peptide is exposed to—e.g., temperature or pH—may impact the peptide's conformational state and, therefore, its stability. *See id.* at 3-8. Stability of peptide formulations is impacted by chemical and physical issues. Ex. 1024 at 8 (Table III). Chemical instabilities affecting certain amino acids of the peptide are dependent on pH and exposure to oxygen, light, high temperature, metal ions, and free radicals. *See, e.g., id.* at 16-25. Physical instabilities like aggregation or precipitation can result from changes to the structure

of the peptide, which can result from, for example, change in pH or temperature, or exposure to certain chemicals. *See, e.g., id.* at 25-29. To ensure that a protein or peptide drug remains safe and effective over its shelf life, the POSAs consider how the drug is to be administered and design formulations that will stabilize the protein.

64. Designing formulations for protein and peptide drugs involves careful consideration of excipients such as buffers, isotonicity agents, as well as others. *See, e.g.,* Ex. 1024 at 16-42. One way to stabilize a peptide drug formulation is to add an excipient known to provide a stabilizing effect to peptide drug products in general, such as propylene glycol. Ex. 1024 at 32-33, Ex. 1026 at 23-24.

65. A POSA would have been aware that excipients can have profound effects on the performance of a drug. As such, it is imperative that parenteral preparations are “of the very best quality and provide the maximum safety for the patient.” *Id.* at 355.

66. Regulatory agencies like the FDA require the role and amount of each excipient to be justified, require the developer to ensure there are no incompatibilities between the excipients and the active drug, and require ongoing quality control of each excipient during manufacturing. Ex. 1029 at 15-36, Ex. 1012 at 258; Ex 1013 at 355-56; Ex. 1024 at 7.

67. Thus, the POSA would have known that it was desirable to keep protein/peptide formulations “as simple as possible...and, if possible, to use

excipients that have previously been used in [FDA]-approved formulations.” Ex. 1024 at 7; Ex. 1005 at 4. Consequently, POSAs knew that it would be preferable to minimize the number of excipients used in a parenteral dosage form. Ex. 1005 at 4, 7; Ex. 1024 at 7; Ex. 1012 at 258.

i. Use of Propylene Glycol in Peptide Formulations

68. Propylene glycol was also a well-known pharmaceutical excipient used in formulations for a wide variety of purposes, including as an “[a]ntimicrobial preservative; disinfectant; humectant; plasticizer; solvent; stabilizer for vitamins; [and] water-miscible cosolvent.” Ex. 1023 at 17; *see also* Ex. 1024 at 32; Ex. 1013 at 312.

69. Propylene glycol was also well known to function as an isotonicity agent in liquid formulations. Ex. 1014 at 10:1-8; Ex. 1025 at 28:24-27; Ex. 1007 at ¶¶[0014]; Ex. 1013 at 312; Ex. 1063 at 4:31-33 (U.S. Patent No. 4,425,346) (“[A]queous solutions ... will contain tonicity adjusting agents, for example sodium chloride, potassium chloride, glycerol, *propylene glycol*, urea or dextrose” and noting that propylene glycol is preferred because it is non-ionic); Ex. 1064 at 4:61-66 (U.S. Patent No. 6,207,684) (“[S]uitable agents which may be utilized to adjust the tonicity or osmolality of the formulations include sodium chloride, potassium chloride, mannitol, dextrose glycerine and *propylene glycol*. Such agents, if utilized, will be employed in an amount of 0.1% to 10.0% by weight (wt. %).”); Ex. 1065 at

7:47-52 (U.S. Patent No. 6,440,460) (“Non-ionic tonicity-enhancing agents are, for example, urea, glycerol, sorbitol, mannitol, *propylene glycol*, or dextrose.”).

70. In addition, propylene glycol—a polyhydric alcohol—was well known as a stabilizer used to prevent aggregation and precipitation in protein formulations. *See* Ex. 1008 at 5; Ex. 1023 at 17; Ex. 1024 at 32; Ex. 1026 at 23-24 (Table 1); Ex. 1019 at, *e.g.*, 10:10-18 (describing propylene glycol as a stabilizing agent), 13:11-17 (“propylene glycol is added to prevent precipitation of [the protein] in solution ... in the concentration range of between 1 - 30% (w/v).”), 23:10-22 (propylene glycol inhibited formation of protein precipitates after physical and heat stresses); Ex. 1024 at 32 (describing propylene glycol as a stabilizing agent). Polyhydric alcohols were known to stabilize proteins in solution in concentrations from 1.0% to 10% (equivalent 10mg/ml to 100mg/ml). Ex. 1026 at 26.

71. Propylene glycol was also known as an anti-microbial preservative and antiseptic similar in effectiveness to ethanol, which is advantageous for multi-use parenteral formulations vulnerable to microbial contamination. Ex. 1023 at 17; Ex. 1013, 28. Other known functions of propylene glycol are as a disinfectant, humectant, plasticizer, and solvent and water-miscible co-solvent. Ex. 1023 at 17; Ex. 1013 at 312.

72. Further, propylene glycol was among a small group particularly acceptable pharmaceutical solvents; Ex. 1061 (Aulton) at 10 (“[t]he most acceptable

non-aqueous solvents pharmaceutically are glycerol, *propylene glycol* and ethanol.”). In addition, propylene glycol was well known as a humectant, which can be incorporated into formulations to reduce water evaporation and prevent drying out. *Id.* at 48.

ii. Propylene Glycol is Safe

73. A POSA also would have known that propylene glycol has a relatively low safety risk. Propylene glycol is included in the FDA Inactive Ingredients Guide (dental preparations, IM and IV injections, inhalations, ophthalmic, oral, otic, percutaneous, rectal, topical and vaginal preparation), and is “generally regarded as a relatively nontoxic material.” Ex. 1022 at 18; Ex. 1023 at 18.

74. A POSA would have been cautioned not to use propylene glycol at high concentrations, because doing so could cause pain or irritation during parenteral administration. Such levels, however, were unlikely to be reached because a mere “2% [by volume] aqueous solution is iso-osmotic with serum.” In other words, there was no reason for a POSA to use propylene glycol in a parenteral formulation at concentrations high enough to potentially cause significant adverse effects. Ex. 1023 at 17; Ex. 1022 at 17; Ex. 1013 at 318.

iii. Propylene Glycol’s Advantages Over Other Isotonic Agents

75. POSAs knew that propylene glycol had advantages over other isotonicity agents like glycerol, polyethylene glycols, mannitol, and other sugars.

For example, propylene glycol would have been preferred over salts due to potential problems with protein stability in the latter. Ex. 1024 at 40. Polyethylene glycols have the potential for forming peroxides that can damage a peptide. Glycerol¹ was known to increase viscosity, which could be problematic for an injectable formulation. On the other hand, propylene glycol was known to be a better general solvent than glycerol and was widely used as an alternative or replacement for glycerin. Ex. 1013 at 28; Ex. 1022 at 17; Ex. 1023, 17.

76. POSAs would also have known that propylene glycol had several advantages over mannitol. A POSA would have known that mannitol is naturally a solid under standard conditions (e.g., at room temperature and atmospheric pressure). *See, e.g.*, Ex. 1023 at 13 (showing mannitol's melting point as 166-168°C). Consistent with it being a solid at room temperature, mannitol was "widely used in pharmaceutical formulations," primarily used "as a diluent (10–90% w/w) in tablet formulations." *Id.* at 12. Each of its most common roles took advantage of mannitol's characteristics as a solid, including its use in direct-compression tablets, chewable formulations, and lyophilized formulations, and as a plasticizer, solid diluent, carrier of dry powders, and bulking agent. *Id.* POSAs knew that mannitol's solubility in aqueous solutions under standard conditions was only about 18-22%

¹ I note that the term "glycerin" is synonymous with "glycerol." *See, e.g.*, Ex. 1022 at 9.

w/v. *See Id.* at 5 (describing mannitol's solubility at 20°C as "1 in 5.5"); Ex. 1010 at 6; Ex. 1009.

77. Further, a POSA would have known use of mannitol at high concentrations in parenteral formulations was risky. This is at least because it "may be salted out by potassium chloride or sodium chloride" at concentrations above 20% w/v, and mannitol was known to precipitate out of solution at a 25% w/v concentration when it contacted plastic, and plastic could be present in the injection mechanism of a parenteral dosage form. *See Id.* at 5; *see also* Ex.1009; Ex. 1011 at 4. A POSA would have known that when a solution containing mannitol evaporates, such as during lyophilization and other water-vapor removal processes, mannitol produces a stiff cake. Ex. 1022 at 12; Ex. 1023 at 12.

78. Moreover, in its dry state, mannitol can be a crystalline powder that is cohesive. Ex. 1022 at 12-13; Ex. 1023 at 13. Furthermore, a POSA would have expected that "[r]educing sugar impurities in mannitol" might destroy a peptide via oxidative mechanisms. *Id.* at 6; Ex. 1062 (Dubost) at 1, 3. Reducing sugar impurities can lead to destructive Maillard reactions with the peptide, i.e., an irreversible chemical reaction occurs between reducing sugars and free amines in peptides and proteins. Ex. 1067 at 11; Ex. 1061 at 60. The POSA also would have known that mannitol can "form complexes with some metals," such as aluminum, copper and

iron. Ex. 1022 at 15; Ex. 1023 at 14. Metals such as iron are found in the stainless steel of injection needles.

79. In contrast, POSAs knew that propylene glycol in its natural state is a liquid solvent under standard conditions (e.g., at room temperature and atmospheric pressure). *See, e.g.*, Ex. 1022 at 17; Ex. 1023 at 17 (showing propylene glycol's melting point as -59°C). Propylene glycol was thus well known by a POSA to be “widely used as a solvent, extractant, and preservative in a variety of parenteral and nonparenteral pharmaceutical formulations,” with the ability to “dissolve[] a wide variety of materials.” *Id.* A POSA would have known that propylene glycol was often used in dosage forms where its liquid characteristics were helpful, including topical preparations, solutions, aerosol solutions, oral solutions, and parenterals. *Id.* In addition, propylene glycol is described as a “clear, colorless, viscous, practically odorless liquid,” in contrast to mannitol's solid state. *Id.* Although certain liquids including water can readily evaporate at ambient conditions, leaving their non-volatile contents behind, the POSA would have known that propylene glycol, in contrast, has a “lack of volatility” that could be beneficial in certain formulations. *Id.* The ability of propylene glycol to hold water and prevent evaporation is well known; about 5% propylene glycol is commonly used in topical formulations to prevent drying out, and in emulsions to prevent evaporation of formulation water from a product container when the closure is removed. Ex. 1061 at 48.

80. The POSA thus knew that propylene glycol had several characteristics making it a favorable and preferred excipient for use in a peptide parenteral formulation.

8. SCOPE AND CONTENT OF THE PRIOR ART REFERENCES

A. Flink (Ex. 1004)

81. International Patent Publication No. WO 03/002136 (“Flink”) (Ex. 1004) was filed on June 27, 2002, and published on January 9, 2003. Flink claims priority to six Danish applications filed between June 28, 2001, and January 18, 2002. Ex. 1004 at 1. Novo Nordisk A/S is listed as Applicant. *Id.* James M. Flink, Silke Moller Larsen, Simon Bjerregaard Jensen, and Dorthe Kot Englund are named as inventors. *Id.*

82. Flink concerns aqueous pharmaceutical formulations of GLP-1 compounds that are physically and chemically stable at high concentrations and have long-term storage potential suitable for parenteral and non-parenteral routes of administration alike. Ex. 1004 at 4:17–30. Flink recognized that there were many different GLP-1 compounds known in the art. *See* Ex. 1004 at 4:38-52 (citing numerous prior art publications; *see* Exs. 1031-45).

83. The Flink specification also recognized the technical challenge of ensuring that protein-based drug products remain stable during their shelf life due to the “inherent lability of macromolecules” and protein sensitivity “to both chemical

and physical degradation” including the breakdown of covalent bonds due to “hydrolysis, racemization, oxidation or crosslinking” and conformational changes including “loss of higher order structure, aggregation, precipitation or adsorption to surfaces.” *Id.* at 3:12–18. Flink also notes that “GLP-1 is known to be prone to instability due to aggregation” and that despite previous formulations designed for stabilizing GLP-1 and GLP-1 analogues, improvements are still needed in the field. *Id.* at 3:18–24.

84. The pharmaceutical formulations disclosed by Flink generally include “a GLP-1 compound, and a buffer, wherein said GLP-1 compound is GLP-1 (7-37) or an analogue thereof wherein an amino acid residue of the parent peptide has a lipophilic substituent attached optionally via a spacer, wherein said GLP-1 compound is present in a concentration from 0.1 mg/ml to 100 mg/ml, and wherein said formulation has a pH from 7.0 to 10.” *Id.* at 4:32–5:2. Flink taught that the buffer may be selected from “sodium acetate, sodium carbonate, citrate, glycylglycine, histidine, glycine, lysine, arginin, sodium dihydrogen phosphate, *disodium hydrogen phosphate*, sodium phosphate, [or] tris(hydroxymethyl)-aminomethan.” *Id.* at 18:27-30 (emphasis added). Flink further disclosed that of these buffers, glycylglycine, sodium dihydrogen phosphate, *disodium hydrogen phosphate*, and sodium phosphate were particularly preferred. *Id.* at 18:30-33.

85. Flink went on to note that the pharmaceutical formulation may include one or more additional ingredients, including an isotonic agent selected from a group “consisting of a salt (e.g. sodium chloride), a polyhydric alcohol (e.g. propyleneglycol, xylitol, mannitol, sorbitol or glycerol), a monosaccharide (e.g. glucose or maltose), a disaccharide [sic] (e.g. sucrose), an amino acid (e.g. L-glycine, L-histidine, arginine, lysine, isoleucine, aspartic acid, tryptophan, threonine), or polyethyleneglycol (e.g. PEG400).” Ex. 1004, 19:34-20:4. Flink cautioned that neither sodium chloride nor mannitol should be used as the isotonicity agent when the formulation has a pH of 7.4. Ex. 1004, 10:9-22. Flink also taught that the pharmaceutical formulation includes other ingredients such as a preservative, an isotonic agent, a chelating agent, a stabilizer, and a surfactant—specific examples of which were provided as alternatives. *Id.* at 19:16–22:30. Flink further noted that the use of preservatives, isotonic agents, chelating agents, stabilizers, and surfactants was “well-known to the skilled person.” *Id.* at 19:30-33, 20:17-19, 20:30-32, 21:24-26, 22:28-30.

86. Flink disclosed seven examples in which formulations of an exemplary GLP-1 compound, Arg34,Lys26(Nε-(γ-Glu(Nα-hexadecanoyl))) (also referred to as “Compound 1”), were evaluated for stability by a visual inspection and turbidity after being stored for various lengths of time. Visual inspections were given a score of 0 to 3, where a score of 0 corresponds to no turbidity and a score of 3 corresponds

to visual turbidity in daylight—which indicates physical instability. Turbidity measurements were made with a nephelometer, which measures particulates in a suspension based on the amount of light scattered, where a score higher than 10 NTU was considered physically unstable. Ex. 1013 at 80. In Example 1, formulations that included GLP-1(7-37) were shown to be stable for less than one day whereas formulations that included Compound 1 were stable for more than 12 weeks:

Compound	Amount	pH	Buffer	Isotonic agent	Preservative	Visual inspection at 5°C (visual score)	Turbidity measurements at 5°C (NTU)
Arg ³⁴ ,Lys ²⁶ (N ¹⁵ -(¹⁴ -Glu(N ¹² -hexadecanoyl))) GLP-1 (7-37).	3 mg/ml	7.9	Disodium hydrogen phosphate	Mannitol 36.9 mg/ml	Phenol 5 mg/ml	1.5 (12 weeks)	0.9 (6 weeks)
GLP1(7-37)	3 mg/ml	7.9	Disodium hydrogen phosphate	Mannitol 36.9 mg/ml	Phenol 5 mg/ml	3 (1 day)	364 (1 day)

Id. at 38.

87. In Example 2, formulations including high concentrations of Compound 1 (80 mg/ml) were shown to be stable for at least 22 months:

Amount of compound 1	PH	Buffer	Visual inspection at 5°C (visual score)	Turbidity measurements at 5°C (NTU)
80 mg/ml	7.4	Disodium hydrogen phosphate	1 (8 months)	4.7 (10 months)
80 mg/ml	7.4	Disodium hydrogen phosphate	1 (22 months)	4.9 (22 months)

Id. at 39.

88. In Example 3, the addition of a preservative (phenol) to the formulations with high concentrations of Compound 1 were also shown to be stable for at least 22 months:

Amount of compound 1	PH	Buffer	Preservative	Visual inspection at 5°C (visual score)	Turbidity measurements at 5°C (NTU)
80 mg/ml	7.4	Disodium hydrogen phosphate	Phenol 10 mg/ml	1 (8 months)	4.3 (10 months)
80 mg/ml	7.4	Disodium hydrogen phosphate	Phenol 10 mg/ml	1 (22 months)	5.3 (22 months)

Id. at 40.

89. In Example 4, formulations that included various concentrations of Compound 1 (0.1 mg/ml, 1 mg/ml, 3 mg/ml, 5 mg/ml), buffers (sodium dihydrogen

phosphate/disodium hydrogen phosphate, glycylglycine, glycine), isotonic agents (mannitol, glycerol), preservatives (phenol, benzylalcohol, m-cresol), and pH levels (7.0, 7.4, 7.8, 7.9, 9.4) were shown to be stable for at least 22 months:

Amount of Compound 1	PH	Buffer	Isotonic agent	Preservative	Visual inspection at 5°C (visual score)	Turbidity measurements at 5°C (NTU)
0.3 mg/ml	7.4	Sodium dihydrogen phosphate/ disodium hydrogen phosphate	Mannitol 36.9 mg/ml	Phenol 5 mg/ml	0 (24 months)	0.6 (24 months)
3 mg/ml	7.9	glycylglycine	Glycerol 16.0 mg/ml	Phenol 5 mg/ml	0.5 (12 weeks)	2.1 (6 weeks)
3 mg/ml	7.9	glycylglycine	Glycerol 16.0 mg/ml	Phenol 5 mg/ml	1 (15 months)	0.7 (15 months)
1 mg/ml	7.0	Sodium dihydrogen phosphate/ disodium hydrogen phosphate	Mannitol 17.0 mg/ml	Benzylalcohol 18 mg/ml	0.5 (9 months)	1.7 (11 months)
1 mg/ml	7.0	Sodium dihydrogen phosphate/ disodium hydrogen phosphate	Mannitol 17.0 mg/ml	Benzylalcohol 18 mg/ml	0.5 (22 months)	1.7 (22 months)
1 mg/ml	7.0	Sodium dihydrogen phosphate/ disodium hydrogen phosphate	Mannitol 38.5 mg/ml	m-cresol (3 mg/ml) and phenol (1.5 mg/ml)	0 (9 months)	1.5 (11 months)

1 mg/ml	7.0	Sodium dihydrogen phosphate/ disodium hydrogen phosphate	Mannitol 38.5 mg/ml	m-cresol (3 mg/ml) and phenol (1.5 mg/ml)	0.5 (22 months)	1.9 (22 months)
5 mg/ml	7.8	Sodium dihydrogen phosphate/ disodium hydrogen phosphate	Mannitol 17.0 mg/ml	Benzylalcohol 18 mg/ml	0.5 (9 months)	1.8 (11 months)
5 mg/ml	7.8	Sodium dihydrogen phosphate/ disodium hydrogen phosphate	Mannitol 17.0 mg/ml	Benzylalcohol 18 mg/ml	1 (22 months)	1.5 (22 months)
3 mg/ml	9.4	glycine	Mannitol 36.9 mg/ml	Phenol 5 mg/ml	0.5 (2½ months)	0.7 (2 months)
3 mg/ml	9.4	glycine	Mannitol 36.9 mg/ml	Phenol 5 mg/ml	1 (14 months)	0.7 (14 months)

Id. at 41-42.

90. In Example 5, the addition of a chelating agent, stabilizer, or surfactant was also shown to result in a product being stable for at least 22 months. In addition, several products that lacked mannitol as an isotonic agent were stable for at least 22 months:

Amount of compound 1	PH	Buffer	Isotonic agent	Preservative	Chelating agent/stabiliser/surfactant	Visual inspection at 5°C (visual score)	Turbidity measurements at 5°C (NTU)
3 mg/ml	9.4	Glycine	Mannitol 36.9 mg/ml	Phenol 5 mg/ml	EDTA (1 mg/ml)/ L-Histidin (1.55 mg/ml)	0.5 (2½ months)	1.2 (2 months)
3 mg/ml	9.4	Glycine	Mannitol 36.9 mg/ml	Phenol 5 mg/ml	EDTA (1 mg/ml)/ L-Histidin (1.55 mg/ml)	0.5 (14 months)	0.9 (14 months)
3 mg/ml	9.4	glycine	Mannitol 36.9 mg/ml	Phenol 5 mg/ml	Poloxamer 188 (4 mg/ml)/ PEG 35000 (30 mg/ml)	1 (2½ months)	1.3 (2 months)
3 mg/ml	9.4	glycine	Mannitol 36.9 mg/ml	Phenol 5 mg/ml	Poloxamer 188 (4 mg/ml)/ PEG 35000 (30 mg/ml)	1 (14 months)	0.8 (14 months)
80 mg/ml	7.4	Disodium hydrogen phosphate	none	none	LPCM 19 mg/ml	0 (8 months)	7.3 (10 months)
80 mg/ml	7.4	Disodium hydrogen phosphate	none	none	LPCM 19 mg/ml	1 (22 months)	8.1 (22 months)

Id. at 43.

91. In Example 6, a formulation was evaluated at different temperatures—5°C, 25°C, and 37°C—and shown to be stable for more than 15 months, more than 12 weeks, and more than 12 weeks, respectively. All the formulations in this example used a polyhydric alcohol as the isotonic agent, specifically glycerol:

Amount of Compound 1	PH	Buffer	Isotonic agent	Preservative	Temp.	Visual inspection (visual score)	Turbidity measurements (NTU)
3 mg/ml	8.4	Disodium hydrogen phosphate	Glycerol 16.0 mg/ml	Phenol 7 mg/ml	5°C	0.5 (12 weeks)	1.0 (6 weeks)
3 mg/ml	8.4	Disodium hydrogen phosphate	Glycerol 16.0 mg/ml	Phenol 7 mg/ml	5°C	1 (15 months)	0.6 (15 months)
3 mg/ml	8.4	Disodium hydrogen phosphate	Glycerol 16.0 mg/ml	Phenol 7 mg/ml	25°C	0.5 (12 weeks)	1.00 (8 weeks)
3 mg/ml	8.4	Disodium hydrogen phosphate	Glycerol 16.0 mg/ml	Phenol 7 mg/ml	37°C	1 (12 weeks)	1.1 (8 weeks)

Id. at 44.

92. In Example 7, formulations including disodium hydrogenphosphate, dihydrate, as a buffer, and certain stabilizers (histidine, arginine and imidazole) displayed improved stability. The first 5 formulations contain mannitol, whereas the last four formulations contain the polyhydric alcohol glycerol, instead, and lack mannitol:

Composition	pH	Temperature	Purity, Compound 1 (%) T = 12 weeks	Dimer formation, Compound 1 (%) T = 12 weeks
3 mg/ml Compound 1 1.42 mg/ml disodium hydrogenphosphate, dihydrate 5 mg/ml phenol 36.9 mg/ml mannitol	7.4	37°C	78.4	5.43
3 mg/ml Compound 1 1.42 mg/ml disodium hydrogenphosphate, dihydrate 5 mg/ml phenol 36.9 mg/ml mannitol 1.55 mg/ml L-histidine	7.4	37°C	85.9	3.28
3 mg/ml Compound 1 1.42 mg/ml disodium hydrogenphosphate, dihydrate 5 mg/ml phenol 36.9 mg/ml mannitol 7.75 mg/ml L-histidine	7.4	37°C	86.2	1.88
3 mg/ml Compound 1 1.42 mg/ml disodium hydrogenphosphate, dihydrate 5 mg/ml phenol 36.9 mg/ml mannitol 1.74 mg/ml L-arginine	7.4	37°C	85.3	3.70
3 mg/ml Compound 1 1.42 mg/ml disodium hydrogenphosphate, dihydrate 5 mg/ml phenol 36.9 mg/ml mannitol 0.68 mg/ml imidazole	7.4	37°C	74.3	3.42
2 mg/ml Compound 1 1.42 mg/ml disodium hydrogenphosphate, dihydrate 5.5 mg/ml phenol	7.7	37°C	88.5	7.74

16 mg/ml glycerol				
2 mg/ml Compound 1	8.0	37°C	88.2	7.62
1.42 mg/ml disodium hydrogenphosphate, dihydrate				
5.5 mg/ml phenol				
16 mg/ml glycerol				
2 mg/ml Compound 1	7.7	37°C	90.4	4.71
1.42 mg/ml disodium hydrogenphosphate, dihydrate				
5.5 mg/ml phenol				
16 mg/ml glycerol				
1.55 mg/ml histidine				
2 mg/ml Compound 1	8.0	37°C	90.6	4.67
1.42 mg/ml disodium hydrogenphosphate, dihydrate				
5.5 mg/ml phenol				
16 mg/ml glycerol				
1.55 mg/ml histidine				

Id. at 45-46.

B. Betz (Ex. 1005)

93. International Patent Publication No. WO 2004/004781 (“Betz”) (Ex. 1005) was filed on July 8, 2003, and published on January 15, 2004. Betz claims priority to three U.S. provisional applications filed on July 9, 2002. Ex. 1005 at 1. Sandoz GmbH and Grandis Biotech GmbH are listed as Applicants. *Id.* Michael Betz and John Stevens are named as inventors. *Id.*

94. Betz concerns multi-dosage, aqueous pharmaceutical formulations for high concentrations of human growth hormone (hGH) that are stable—i.e., that exhibit minimal or no crystallization, aggregation, or degradation—when stored inside a refrigerator for at least several months or when stored outside of a refrigerator for at least several hours or longer. Ex. 1005 at 5.

95. Like Flink, Betz recognized that a “long appreciated problem with aqueous liquid formulations of pharmaceutical proteins, not just hGH, is that of instability during storage over a period of time.” *Id.* at 3. Betz also noted that care must be taken to ensure that excipients used as stabilizers to address instability problems are clinically acceptable and that “any unnecessary additives / excipients, particularly synthetic additives / excipients, must be avoided in order to reduce risks to patients.” *Id.* at 4. To that end, Betz taught that propylene glycol is a “favourable parameter regarding stability” and that by using propylene glycol, “it [was] surprisingly established that a stable formulation can be composed of a smaller number of excipients than previously thought.” *Id.* at 5-6.

96. As Betz further indicated, propylene glycol not only acts as a stabilizer in the formulations, but “simultaneously, it contributes to the desired tonicity of the formulation.” *Id.* at 6. In fact, Betz taught that it would be preferred for “1,2-propylene glycol, together with the further excipients [sic], is capable of providing the desired tonicity without the need of an additional tonicity-adjusting agent to be present, thereby keeping the overall number of excipients to be used to a minimum.” *Id.* at 7.

97. Betz discloses eight examples of pharmaceutical formulations that include propylene glycol as a stabilizing agent:

Formulation (in water for injection)	1	2	3	4	5
Human Growth Hormone	6,67 mg/ml	6,67 mg/ml	6,67 mg/ml	6,67 mg/ml	6,67 mg/ml
Na ₂ HPO ₄ x 7 H ₂ O [Ⓢ]	0.49 mg/ml	0.49 mg/ml	0.49 mg/ml	0.49 mg/ml	0.49 mg/ml
NaH ₂ PO ₄ x 2 H ₂ O [Ⓢ]	1.29 mg/ml	1.29 mg/ml	1.29 mg/ml	1.29 mg/ml	1.29 mg/ml
Benzyl Alcohol	9.0 mg/ml	9.0 mg/ml	9.0 mg/ml	9.0 mg/ml	9.0 mg/ml

Poloxamer 188	2.00 mg/ml	2.00 mg/ml	2.00 mg/ml	2.00 mg/ml	2.00 mg/ml
Mannitol	27.4mg/ml	25.0mg/ml	22.5 mg/ml	15.2 mg/ml	8.1 mg/ml
Glycine	---	---	---	---	---
1,2-Propylene Glycol	1.0 mg/ml	2.0 mg/ml	3.0 mg/ml	6.0 mg/ml	9.0 mg/ml
pH	6.2	6.2	6.2	6.2	6.2
[Ⓢ] Including the phosphate from the hGH bulk solution.					

Formulation	6	7	8
Human Growth Hormone	6,67 mg/ml	6,67 mg/ml	6,67 mg/ml
Na ₂ HPO ₄ x 7 H ₂ O [Ⓢ]	0.49 mg/ml	0.89 mg/ml	0.89 mg/ml
NaH ₂ PO ₄ x 2 H ₂ O [Ⓢ]	1.29 mg/ml	1.05 mg/ml	1.05 mg/ml
Benzyl Alcohol	9.0 mg/ml	9.0 mg/ml	9.0 mg/ml
Poloxamer 188	2.00 mg/ml	2.00 mg/ml	2.00 mg/ml
Mannitol	---	---	---
Glycine	---	---	7.5 mg/ml
1,2-Propylene Glycol	12.4 mg/ml	15 mg/ml	7.5 mg/ml
pH	6.2	6.2	6.2
[Ⓢ] Including the phosphate from the hGH bulk solution.			

Id. at 18-19.

98. Two of the formulations disclosed by Betz (Formulations 6 and 7) do not include an additional tonicity-adjusting agent—and neither shows crystallization for at least 7 weeks when stored at temperatures of 15°C, and 25°C. Ex. 1005 at 18. In contrast, formulations 1 to 4 contain both mannitol and propylene glycol, and a lack of crystallization is reported only up through 4 weeks at 15°C or 25°C. *Id.* In particular, formulation 1 contains mannitol at about 27.4 mg/mL, and although the example does not explicitly specify that 27.4 mg/mL mannitol was the isotonicity

agent, the specification states that “[i]n a particularly preferred embodiment thereof, the additional tonicity-adjusting agent is mannitol at a concentration of about 30 mg/ml.” *Id.* at 11.

C. Other Art That Informs the Person of Ordinary Skill’s Knowledge

i. U.S. Patent No. 6,268,343 (“Knudsen I”) (Ex. 1006)

99. U.S. Patent No. 6,268,343 (“Knudsen I”) (Ex. 1006) was filed on February 26, 1999. Knudsen I issued on July 31, 2001, prior to the earliest priority date for the ’833 patent. Novo Nordisk A/S is listed as the Assignee. Ex. 1006 at (73). Liselotte Bjerre Knudsen, Per Olaf Huusfeldt, Per Franklin Nielsen, Niels C. Kaarsholm, Helle Birk Olsen, Søren Erik Bjørn, Freddy Zimmerdahl Pedersen, and Kjeld Madsen are named as the inventors.

100. Knudsen I disclosed numerous derivatives of human GLP-1 and fragments and/or analogues thereof, including liraglutide. Knudsen I further disclosed formulations that include a GLP-1 compound (e.g., liraglutide), a buffer (e.g., phosphate buffer), an isotonic agent (e.g., mannitol), and a preservative (e.g., phenol). Ex. 1006 at 168:1-6, 216:58-217:20.

ii. Eur. Patent. App. Pub. No. EP0923950 (“Ibaraki”) (Ex. 1007)

101. European Patent Application Publication No. EP0923950 (“Ibaraki,” Ex. 1007) was filed on December 18, 1998. Ibaraki published on June 23, 1999, prior to the earliest priority date for the ’833 patent. Ibaraki claims priority to two

Japanese applications filed on December 18, 1997, and October 30, 1998. Ex. 1007 at 1. Tomey Corporation is listed as the Applicant. *Id.* Keiko Ibaraki, Hideto Mizuno, Takehiko Goshima, and Keiko Shimbo are named as the inventors. *Id.*

102. Ibaraki relates to liquid ophthalmic formulations for contact lenses that include a cation polymer with antimicrobial or disinfecting effects. *Id.* at ¶¶[0009]-[0010]. Ibaraki also notes that the addition of a nonionic tonicity agent like glycerin, propylene glycol, or mannitol can enhance the antimicrobial activity of the cation polymer. *Id.* at ¶[0014].

iii. Powell (Ex. 1008)

103. Powell et al., “Parenteral Peptide Formulations: Chemical and Physical Properties of Native Luteinizing Hormone-Releasing Hormone (LHRH) and Hydrophobic Analogues in Aqueous Solution,” *Pharmaceutical Research*, Vol. 8, No. 10 (1991) (“Powell”) (Ex. 1008) is a journal article from 1991, published prior to the earliest priority date of the ’833 patent.

104. Powell disclosed parenteral peptide formulations for the LHRH analogs nafarelin and detirelix. In Powell, it was shown that nafarelin and detirelix aggregate readily to form crystals in aqueous solution, but that the addition of propylene glycol “raises the minimum concentration for peptide aggregation, and thus, many of the potential problems associated with aggregate formation may be minimized or eradicated.” Ex. 1008, 5.

iv. Epperson (Ex. 1009)

105. E. Epperson, “Mannitol Crystallization in Plastic Containers,” 35 *Am. J. Hosp. Pharm.* 1337 (1978) (“Epperson”) (Ex. 1009) is a letter published in a journal published in November 1978 and prior to the earliest priority date for the ’833 patent.

106. Epperson relates to a letter written by the Assistant Director of Pharmacy Affairs at a hospital, reporting that a 25% mannitol injection given over the course of 30 minutes exhibited a “a very heavy, white flocculent precipitate” that was reproducible at temperatures above 75 degrees Fahrenheit. Ex. 1009.

v. Jacobs (Ex. 1011)

107. J. Jacobs, “Factors Influencing Drug Stability in Intravenous Infusions,” 27 *J. Hosp. Pharm.* 341 (Dec. 1969) (“Jacobs”) (Ex. 1011) is an article published in December 1969 and prior to the earliest priority date for the ’833 patent.

108. Jacobs is related to a two month survey of the use of intravenous drugs at a hospital in Israel. Jacobs reports that “[i]nfusion fluids may have to be warmed to 37°C to ensure that the solids are completely dissolved and that the solution is homogenous, e.g., 25% mannitol” and that “[s]upersaturated solutions can be readily crystallised out and it is recommended that no additions be made to mannitol.” Ex. 1011 at 4.

vi. Int'l Patent Pub. No. WO 1999/040788 ("Young") (Ex. 1025)

109. International Patent Publication No. WO 99/40788 ("Young," Ex. 1025) was filed on February 5, 1999. Young published on August 19, 1999, prior to the earliest priority date for the '833 patent. Young claims priority to a provisional application filed on February 13, 1998. Ex. 1025 at 1. Amylin Pharmaceuticals, Inc. is listed as the Applicant. *Id.* Andrew A. Young, Will Vine, Nigel R.A. Beeley, and Kathryn Prickett are named as the inventors. *Id.*

110. Young relates to parenteral formulations of GLP-1, GLP-1 agonists, exendin, or exendin agonists that have diuretic and inotropic effects. *Id.* at 8:23–31. Young notes that GLP-1 agonist compounds are preferably "suspended in an aqueous carrier, for example, in an isotonic buffer solution" where "[t]he desired isotonicity may be accomplished using sodium chloride or other pharmaceutically acceptable agents such as dextrose, boric acid, sodium tartrate, propylene glycol, polyols (such as mannitol and sorbitol), or other inorganic or organic solutes." *Id.* at 28:12–27. U.S. Patent No. 8,759,291 (Ex. 1017) claims priority to Young and has the same disclosure.

vii. Int'l Patent Pub. No. WO 03/072195 ("Khan") (Ex. 1014)

111. International Patent Publication No. WO 03/072195 ("Khan") (Ex. 1014) was filed on February 7, 2003. Khan published on September 4, 2003, prior to the earliest priority date for the '833 patent. Khan claims priority to a provisional

application filed on February 20, 2002. Ex. 1014 at 1. Eli Lilly and Company is listed as the Applicant. *Id.* Mohamed Amin Khan is the named inventor. *Id.*

112. Khan relates to formulations of GLP-1 compounds that can be administered orally. *Id.* at 4:3-13. The oral formulations may include propylene glycol. *Id.* at 10:1–8. U.S. Patent Application Publication No. US 2005/0148497 (Ex. 1018) claims priority to Khan and has the same disclosure.

viii. Int'l Patent Pub. NO. WO 95/022560 ("Dix") (Ex. 1019)

113. International Publication No. WO 95/22560 ("Dix") (Ex. 1019) was filed on February 21, 1995. Dix published on August 24, 1995, prior to the earliest priority date for the '833 patent. The Syntex-Synergen Neuroscience Joint Venture is listed as the Applicant. Ex. 1019 at 1. Daniel Dix, Andrew A. Kosky, and Erwin Freund are named as inventors. *Id.*

114. Dix discloses pharmaceutical formulations of ciliary neurotrophic factor (CNTF) for treatment of peripheral nervous system damage, wherein the formulations are suitable for maintaining stability and bioactivity in aqueous solution for a prolonged period. *Id.* at 9:23-37. Dix teaches formulations in which "propylene glycol is added to prevent precipitation of CNTF in solution," in the "concentration range of between 1 – 30% (w/v)," and includes results of testing propylene glycol's ability to stabilize CNTF in solution. Ex. 1019 at 13, 23-24 (Example 4).

ix. U.S. Patent No. 6,458,924 (“Knudsen II”) (Ex. 1020)

115. U.S. Patent No. 6,458,924 (“Knudsen II”) was filed on September 16, 1999. Knudsen II issued on October 1, 2002, prior to the earliest priority date for the ’833 patent. Novo Nordisk A/S is listed as the Assignee. Ex. 1020 at (73). Liselotte Bjerre Knudsen, Per Olaf Huusfeldt, and Per Franklin Nielsen are named as the inventors. *Id.* at (75).

116. Like Knudsen I, Knudsen II discloses numerous derivatives of human GLP-1 and fragment and/or analogues thereof, including liraglutide. Knudsen II also discloses formulations that include a GLP-1 compound (e.g., liraglutide), a buffer (e.g., phosphate buffer), an isotonic agent (e.g., sodium chloride, mannitol, or glycerol), and a preservative (e.g., phenol). Ex. 1020 at 153:46-56.

x. Int’l Patent Pub. NO. WO 00/037098 (Ex. 1021)

117. International Publication No. WO 00/37098 A1, Shelf-Stable Formulation of Glucagon-Like Peptide-1 (published June 29, 2000), was filed on December 21, 1999, with priority to Application No. 60/113,499, filed on December 22, 1998, prior to the earliest priority date for the ’833 patent. Eli Lilly and Company is listed as the Applicant. Ex. 1021 at 1. Mark Brader and Allen Pekar are listed as inventors. *Id.*

118. Brader discloses shelf stable formulations of a GLP-1 compound, a preservative (e.g. phenol), a tonicity modifier (e.g. glycerol), and a buffer (e.g.

TRIS). Brader acknowledges that “[t]he long-term stability of peptides, particularly GLP-1, as components of a pharmaceutical composition for administration to mammals, is questionable” and that “[s]uch a lack of stability adversely affects bioavailability.” *Id.* at 3-4.

xi. Handbook of Pharmaceutical Excipients 2000, 2003 (Exs. 1022-1023)

119. Handbook of Pharmaceutical Excipients (Arthur H. Kibbe ed., 3rd ed. 2000) (“Handbook 2000”) (Ex. 1022) and *Handbook of Pharmaceutical Excipients* (Raymond C. Rowe et al. eds., 4th ed. 2003) (“Handbook 2003”) (Ex. 1023) are reference books published in 2000 and 2003, respectively.

120. Handbook 2000 and 2003 are reference guides for formulation scientists that include entries for all well-known excipients used in pharmaceutical formulations, including disodium phosphate dihydrate, glycerin (aka “glycerol”), mannitol, and propylene glycol.

xii. Nail & Akers (Ex. 1024)

121. *Development and Manufacture of Protein Pharmaceuticals*, Nail SL and Akers MJ, eds., Kluwer Academic / Plenum Publishers, New York, 2002, (“Nail & Akers”) (Ex. 1024) is a book related to practices involved with formulation and production of protein drugs that was published in 2002 and prior to the earliest priority date for the ’833 patent.

122. Nail & Akers addresses well-known stability problems that arise when developing a protein drug formulation, including degradation mechanisms like hydrolysis, oxidation, racemization, and interaction with solutes and surfaces; and physical instability issues like denaturation, aggregation, and adsorption. Ex. 1024 at 4-5, 34-36. To help ameliorate those issues, Nail & Akers provides several well known factors and approaches, including the effect of pH and buffers, the addition of excipients that act as stabilizers, the addition of antimicrobial preservatives, and the addition of solubilizing and tonicity agents. *See Id.* at 16-21, 29-42. For example, Nail & Akers teaches that a “formulation scientist can select from a wide variety of excipients that can be effective in stabilizing proteins against denaturation due to extremes in temperature,” examples of which include “[m]annitol (polyol), propylene glycol and polyethylene glycol (polyhydric alcohols), and sucrose, lactose, trehalose, and maltose (dissacharides).” *Id.* at 32. Nail & Akers also notes that “solubility may be improved by the use of solubilizing agents such as glycerin, propylene glycol, polyethylene glycol (300 or 400), and ethanol.” *Id.* at 41. Nail & Akers also notes that the packaging system is an important factor to consider with respect to the compatibility of a parenteral protein drug product and the device or material used. *See Id.* at 42-55. Akers also states that “[t]he best formulation strategy is to keep the formulation as simple as possible, to have a clear reason for including

each additive, and, if possible, to use excipients that have previous been used in Food and Drug Administration (FDA)-approved formulations.” *See Id.* at 7.

123. Nail & Akers also addresses the type of studies that should be performed to comport with ICH² guidelines to ensure quality and stability of the final formulation. *See Id.* at 62-70. For example, guidance for testing stability under storage conditions in a particular container, indicates that studies “should include samples maintained in inverted or horizontal position” and should generate data “that demonstrate that the closure used for multiple-dose application is capable of withstanding repeated insertions and withdrawals so that product retains full potency, purity, and quality.” *Id.* at 65 (Table XVI). Additional guidance includes including studies for evaluating the “[v]isual appearance, visible particulates in ready-to-use or reconstituted solutions” as well as monitoring “[a]dditives such a stabilizers and preservatives that may degrade during the dating period of the product and might adversely affect product quality.” *Id.*

124. Nail & Akers also indicates that parenteral final product lots should be visually inspected to evaluate the solution color and clarity and to determine whether the container is defective or contains particles of foreign matter. *Id.* at 98. Defective

² “ICH” is short for International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use.

containers are removed and rejected, the number and basis for which should be memorialized for quality control. *Id.* at 98-99.

125. Nail & Akers further discusses strategies for studying adsorption of the formulation to the container or the process equipment. *Id.* at 119-125. Noting that there are a number of ways to study equipment adsorption, Nail & Akers suggest exposing small quantities of the formulation to scaled-down equipment or small pieces (or “coupons”) of the material used in the full-scale equipment for periods of time in order to detect adsorption of any component of the formulation. *Id.* at 120-121.

xiii. Bontempo (Ex. 1026)

126. *Development of Biopharmaceutical Parenteral Dosage Forms*, (John A. Bontempo ed., 1997) (“Bontempo”) (Ex. 1026) is a book related to practices involved with formulation and production of protein drugs that was published in 1997 and prior to the earliest priority date for the ’833 patent.

127. Bontempo addressed the requirements for developing pharmaceutical formulations, including the major considerations to be taken into account when designing a formulation. Those considerations include (i) ensuring that the drug has been well-characterized and is reproducible on a scaled-up basis, (ii) the effect of pH on the formulation, (iii) the use of stabilizers, surfactants, polyols, and antioxidants in protein formulations, (iv) selecting a suitable buffer, (v) the use of

antimicrobials or preservatives in the formulation, and (vi) tonicity of the formulation. Ex. 1026 at 22-29. Bontempo noted that propylene glycol is a common stabilizer used in protein formulations. *Id.* at 24 (see Table 1). Further, Bontempo noted that polyols, which include polyhydric alcohols, are found to stabilize proteins in solution in varying concentration from 1.0 to 10%. *Id.* at 26.

128. Further, Bontempo states that “[p]arenteral injectables are most desirable as isotonic solutions” and that “[i]n controlling isotonicity, we can control tissue damage irritation, pain, hemolysis, and crenation of the red blood cells.” *Id.* at 29.

129. Bontempo also addresses several tests and conditions to ensure the formulation is stable and can endure the formulation can endure shipping conditions, freeze-thaw cycles, certain storage positions (e.g., upright, inverted and horizontal), and mechanical stresses. *Id.* at 33-39. Bontempo notes that it is necessary to develop at least two “stability-indicating” assays for that those purposes. Bontempo also states that the bulk active drug substance must be tested for stability to assess how long the formulation can be stored, and at what temperature. *Id.*

xiv. Gatlin (Ex. 1027)

130. Gatlin, “Formulation and Administration Techniques to Minimize Injection Pain and Tissue Damage Associated with Parenteral Products” in

Injectable Drug Development (1999) (“Gatlin”) (Ex. 1027) is a book chapter published in 1999, prior to the earliest priority date for the ’833 patent.

131. Gatlin provides strategies to develop a parental product, with emphasis “placed on the two formulation parameters, pH and tonicity, that are usually associated with tissue damage and injection pain.” *Id.* at 13. Gatlin notes that at the preformulation stage, studies should be developed to address interactions of the drug with excipients, solvents, packaging materials and biological systems. *Id.* at 14. Further, assays should be developed for preformulation physiochemical properties including: molecular weight; color; particle size, shape and crystallinity; thermal characteristics of melting and thermal profiles; hygroscopicity; absorbance spectra; solubility in selected solvents (water, ethanol, propylene glycol, polyethylene glycol 400, plus others as needed); pH solubility profile; temperature solubility profile; partition coefficients; stability in selected solvents and pH-dependent stability; ionization constant; and optical activity. *Id.* at 15. In addition, for protein drugs, assays should be developed for physical stability (aggregation), chemical stability (e.g. beta-elimination, deamidation, isomerization/cyclization, oxidation and thiol disulfide exchange) and analytical methods (e.g. fluorescent spectroscopy, electrophoresis, calorimetry, size exclusion chromatography, HPLC, circular dichroism, mass spectrometry and light scattering). *Id.* at 16. Gatlin notes that “[d]ue to the location of human pain receptors, formulation approaches to reduce pain are

more critical for subcutaneous (SC) and intradermal injections and less critical for intramuscular (IM) and intravenous (IV) administration.” *Id.* at 17. Gatlin then provides lists of common excipients used in parenteral formulations and the amounts or ranges they are used at, including phosphoric acid as a buffer for pH 2-3.1 and 6.2-8.2 and phenol as an antimicrobial at about 0.5%. *Id.* at 19-20.

132. Gatlin then addresses the role of formulation tonicity in reducing injection pain and tissue irritation, noting that whereas patients’ injection pain is difficult to assess clinically or to evaluate preclinically, “osmolality and pH are easy to measure.” *Id.* at 22. Further, the “primary purpose for adjusting product osmolality is to minimize red blood cell lysis, tissue damage, and pain when the product is administered” and “aqueous solutions for SC, intradermal, or IM injections should be made isotonic if possible.” *Id.* at 23. Gatlin teaches that iso- osmolality can be determined by freezing point depression or vapor pressure reduction, but also by direct biological methods such as erythrocyte hemolysis. *Id.* at 23-24. Gatlin indicates that common tonicity adjusting agents include mannitol, but other agents such as glycerin and propylene glycol can also affect product tonicity. *Id.* at 23. Gatlin also teaches that co-solvents, including ethanol, propylene glycol, polyethylene glycol and glycerin, can enhance drug solubility and stability, but cautions that concentrations of 20-40% v/v can cause myotoxicity (i.e., muscle tissue). *Id.* at 26.

xv. Remington's 1990 (Ex. 1013)

133. *Remington's Pharmaceutical Sciences* (Alfonso R. Gennaro ed., 18th ed. 1990) ("Remington's 1990") (Ex. 1013) is a book that was published in 1990 and prior to the earliest priority date for the '833 patent.

134. Remington's 1990 is a treatise and reference related to the pharmaceutical sciences, including information on the properties, formulation and manufacturing of pharmaceutical agents. For example, Remington's 1990 provides a guide to the variables and calculations that should be considered when developing drug formulations such as common buffers, excipients, route of administration, and conditions that are commonly considered for improving a drug's stability and safety. *See, e.g.*, Ex. 1013 at 16-55, 220-63, 354-62.

135. Remington's 1990 acknowledges that proteins and peptides present unique challenges when it comes to drug development due to problems that can arise with degradation and other instability issues. *Id.* at 293-94. To deal with that, Remington's 1990 notes that "[p]roteins and peptides can be stabilized in many ways, usually employing empirical, rather than theoretical, procedures" and that "[f]or parenteral formulations, excipients are added to enhance stability." *Id.* at 294. Remington's 1990 also notes that the tonicity of parenteral formulations is an important consideration to avoid pain upon and other unwanted side effects upon injection or infusion and provides calculations for determining an ingredient's

contribution to tonicity. *Id.* at 305-07. Further, while Remington's 1990 recognizes that there may be occasions where interactions between a drug and certain additives, "preliminary screening of commonly used excipients with new-drug substances has become routine in preformulation studies." *Id.* at 294.

136. One common excipient recognized by Remington's 1990 is propylene glycol, which is used for many purposes in formulations. Propylene glycol is known to act as a solvent, preservative, and humectant; and can be used as a diluting agent for injections. *Id.* at 237, 251. Propylene glycol has been used widely as a substitute for glycerin, and is reported to be as effective as ethyl alcohol in its power of inhibiting mold growth and fermentation. *Id.* at 28. Propylene glycol is a humectant, useful to prevent evaporation and retain moisture in formulations. *Id.* at 246, 251. Remington's 1990 also notes that propylene glycol may have an effect on the freezing-point depression and and/or the tonicity of a formulation when present as part of the solvent. *Id.* at 312. Remington's 1990 also shows methods for calculating equivalent amounts of different osmolarity adjusting agents, e.g., substituting boric acid for sodium chloride as a tonicity agent in an eyewash, and states "[t]he same type of calculation may be used for other solutions that are to be made isotonic." *Id.* at 313-14. Finally, Remington's 1990 discusses that tonicity may be tested by observing erythrocyte changes, i.e., testing for hemolysis or marked change in erythrocyte appearance, as this is the ultimate and most direct method of determining

whether a solution is isotonic, as some solutes in sufficient concentration to be iso-osmotic may not be isotonic (e.g., boric acid, ammonium chloride, urea, glycerin and propylene glycol). *Id.* at 305, 311-12.

xvi. Sturis (Ex. 1046)

137. J. Sturis et al., “GLP-1 derivative liraglutide in rats with β -cell deficiencies: influence of metabolic state on β -cell mass dynamics,” *British Journal of Pharmacology* volume 140, 123–132 (2003) (“Sturis”) (Ex. 1046) is a paper that was published on July 29, 2003, prior to the earliest priority date for the ’833 patent.

138. Sturis relates to a study that looked at the effect of liraglutide (Arg³⁴Lys²⁶-(N- ϵ -(γ -Glu(N- α -hexadecanoyl)))-GLP-1(7-37)), also known as NN2211, on glycemia and β -cell mass in two β -cell deficient rat models. Ex. 1046 at 2. Sturis found that liraglutide attenuated diabetes development in prediabetic rats and had antihyperglycemic effects in partially pancreatectomized rats. Those effects were at least in part due to liraglutide’s actions as a GLP-1 agonist but may also depend on the glycemic state of the animal. Liraglutide was given subcutaneously to the animals. *Id.* at 2.

xvii. Chang (Ex. 1059)

139. X. Chang et al., “NMR studies of the aggregation of glucagon-like peptide-1: formation of a symmetric helical dimer,” *FEBS Letters* volume 515, 165–

170 (2002) (“Chang”) (Ex. 1059) is a paper that was published on February 27, 2002, and prior to the earliest priority date for the ’833 patent.

140. Chang notes that GLP-1 “suffers from both metabolic and physical instability.” Ex. 1059 at 1. Chang thus performed studies to investigate the conformation of aggregated GLP-1 in water and 2,2,2-trifluoroethanol (TFE) solutions using nuclear magnetic resonance spectroscopy (NMR) to better understand the propensity of GLP-1 to aggregate in solution. *Id.*

xviii. U.S. Patent No. 4,425,346 (“Horlington”) (Ex. 1063)

141. U.S. Patent No. 4,425,346 (“Horlington”) (Ex. 1063) was filed on January 25, 1982. Horlington issued on January 10, 1984, prior to the earliest priority date for the ’833 patent. Smith and Nephew Associated Companies Limited is listed as the Assignee. Ex. 1063 at (73). Michael Horlington is named as the sole inventor. *Id.* at (75).

142. Horlington discloses aqueous anti-glaucoma ophthalmic solutions that “contain tonicity adjusting agents, for example sodium chloride, potassium chloride, glycerol, propylene glycol, urea or dextrose to render the solution or suspension isotonic or substantially isotonic with tear fluid.” *Id.* at 4:21-26. Horlington also notes that in some cases, “it is preferred that a non-ionic tonicity adjusting agent such as glycerol or propylene glycol is used.” *Id.* at 4:31-33.

xix. U.S. Patent No. 6,207,684 (“Aberg”) (Ex. 1064)

143. U.S. Patent No. 6,207,684 (“Aberg”) (Ex. 1064) was filed on December 2, 1999. Aberg issued on March 27, 2001, prior to the earliest priority date for the ’833 patent. Bridge Pharma, Inc. is listed as the Assignee. Ex. 1064 at (73). A.K. Gunnar Aberg is named as the sole inventor. *Id.* at (75).

144. Aberg discloses for treating ocular diseases using compositions for topical administration including “solutions, suspensions, droplets, sprays, ointments and powders.” *Id.* at 4:48-50. The composition can include tonicity agents, “which may be utilized to adjust the tonicity or osmolality of the formulations,” examples of which include “sodium chloride, potassium chloride, mannitol, dextrose glycerine and propylene glycol” and “if utilized, will be employed in an amount of 0.1% to 10.0% by weight (wt. %).” *Id.* at 4:61-66.

xx. U.S. Patent No. 6,440,460 (“Gurny”) (Ex. 1065)

145. U.S. Patent No. 6,440,460 (“Gurny”) (Ex 1065) was filed on July 27, 1998. Gurny issued on August 27, 2002, prior to the earliest priority date for the ’833 patent. Allergan Sales, Inc. is listed as the Applicant. Ex. 1065 at (73). Robert Gurny, Monia Zignani, and Cyrus Tabatabay are named as inventors. *Id.* at (75).

146. Gurny discloses pharmaceutical compositions for the controlled release of therapeutic agents from a polymer that are preferably administered intramuscularly, subcutaneously or intraocularly. Ex. 1065 at 7:19-21. Gurny

teaches that the compositions can include “tonicity-increasing agents.” Non-ionic tonicity-enhancing agents that may be used “are, for example, urea, glycerol, sorbitol, mannitol, propylene glycol, or dextrose.” *Id.* at 7:50-52.

xxi. Additional Prior Art References and Knowledge

147. In addition to the prior art references summarized above, my declaration addresses additional prior art explaining and confirming the general knowledge of skilled artisans on or before November 20, 2003, the priority date listed on the face of the issued patent (see ¶28). Those and additional publications may also be cited and discussed throughout this declaration. Further, any references referred to in this declaration that were publicly available prior to the priority date of the '833 patent were within the scope of the prior art. Moreover, in this declaration I draw upon the knowledge and expertise that skilled artisans would have had in the relevant field.

9. UNPATENTABILITY OF THE '833 PATENT

A. Claims 1-15 of the '833 Patent Were Anticipated by or Would Have Been Obvious Over Flink

i. Claim 1 Was Anticipated by or Would have Been Obvious Over Flink

148. Claim 1 of the '833 patent recites a pharmaceutical formulation having a pH of from about 7.0 to about 10.0 that includes a GLP-1 agonist, a disodium phosphate dihydrate buffer and propylene glycol in a final concentration of from about 1 mg/ml to about 100 mg/ml.

149. In my opinion, the claims of Flink, in view of Flink's disclosure, anticipates or makes obvious claim 1 of the '833 patent. In particular, claim 14, which I understand is a dependent claim that requires all elements of the claims from which it depends. Here, claim 14 of Flink depends from several claims, including independent claim 5 and dependent claims 6, 8, 10, 11, 12, and 13. Those claims are reproduced below:

5. A *pharmaceutical formulation* comprising an aqueous solution of *a GLP-1 compound*, and *a buffer*, wherein said GLP- 1 compound is *GLP-1 (7-37) or an analogue thereof* wherein an amino acid residue of the parent peptide has a lipophilic substituent attached optionally via a spacer, wherein said GLP-1 compound is present in a concentration from 0.1 mg/ml to 100 mg/ml, and wherein said formulation has a *pH from 7.0 to 10*; provided that if an isotonic agent is present and pH is 7.4 then mannitol or NaCl is not the isotonic agent.

6. The formulation according to claim 5, wherein said GLP- 1 compound is present in a concentration from 1 mg/ml to 100 mg/ml.

8. The formulation according to any one of claims 4 and 6, *wherein said formulation has a pH from 7.5 to 10*.

10. The formulation according to any one of claims 2, 4, 6 and 8, wherein the GLP-1 compound is present in a concentration from 1mg/ml to 80mg/ml, 1mg/ml to 50mg/ml, 1mg/ml to 20mg/ml, 1mg/ml to 10mg/ml, typically from 1-5mg/ml.

11. The formulation according to any one of claims 1-10, further comprising a preservative.

12. The formulation according to claim 11, wherein said preservative is present in a concentration from 0.1mg/ml to 20mg/ml.

13. The formulation according to any one of claims 1-12, further comprising an *isotonic agent*.

14. The formulation according to claim 13, *wherein said isotonic agent is present in a concentration from 1mg/ml to 50mg/ml*.

150. The elements of claim 14 disclose “a pharmaceutical formulation” that includes each element of claim 1 of the '833 patent are in bold italics.

1. Flink disclosed the GLP-1 agonist

151. 151. First, claim 14 of Flink disclosed “a GLP-1 compound...wherein the GLP-1 compound is GLP-1(7-37) or an analogue thereof.” One example of a GLP1- (7-37) analogue disclosed by Flink is Arg³⁴,Lys²⁶(N-ε-(γ-Glu(N-α-hexadecanoyl))))GLP-1 (7-37), which I understand to be the chemical name for liraglutide (also known as NN2211), a known GLP-1 agonist. Ex. 1046 at 2. Liraglutide is also referred to as “Compound 1” in the working examples of Flink. Ex. 1004, 37:26–28, 38-46 (Examples 1-7). Thus, Flink discloses the claimed GLP-1 agonist.

2. Flink disclosed the claimed buffer

152. 152. Second, claim 14 of Flink disclosed a buffer. The formulations disclosed in Example 7 of Flink specifically contain “disodium hydrogenphosphate,

dihydrate” at a concentration of 1.42 mg/ml, which a person of ordinary skill would understand to be an acceptable buffer for the claimed formulations. Ex. 1004, 45–

15. Thus, Flink expressly disclosed the claimed buffer.

153. Flink’s disclosure further states that “disodium hydrogen phosphate” is one of the preferred buffers disclosed as part of a small group of buffers that would have been an acceptable buffer within the scope of claim 14. *See, e.g.*, Ex. 1004, 18:27-33 (“[i]n a preferred embodiment of the invention the buffer is glycylglycine, sodium dihydrogen phosphate, disodium hydrogen phosphate, sodium phosphate or mixtures thereof”). Disodium hydrogen phosphate is a physiological buffer commonly used in phosphate buffers, which are one of the “most frequently employed” buffers along with citrates and acetates. Ex. 1013 at 359.

154. A person of ordinary skill would have understood that a “disodium hydrogen phosphate” buffer is of the same species as a “disodium phosphate dihydrate”³ buffer, and will result in the same pH when added to water, but the hydration state of disodium hydrogen phosphate is ambiguous. Disodium hydrogen

³ The species “disodium phosphate dihydrate” (chemical formula $[\text{Na}_2\text{HPO}_4 \cdot 2\text{H}_2\text{O}]$; molecular weight 156.01 g/mol, CAS 10028-24-7) is a non-ambiguous species of disodium hydrogen phosphate. Other synonyms for disodium phosphate dihydrate include “dibasic sodium phosphate,” “dibasic hydrogen phosphate,” “disodium hydrogen phosphate, dihydrate,” “disodium hydrogenphosphate, dihydrate,” “disodiumphosphate, dihydrate,” “disodium hydrogen phosphate dihydrate,” and “sodium phosphate dibasic dihydrate.” Ex. 1023 at 20.

phosphate may be anhydrous (Na_2HPO_4 , CAS 7558-79-4, 141.96 g/mol), monohydrate ($\text{Na}_2\text{HPO}_4 \cdot \text{H}_2\text{O}$, CAS 118830-14-1, 159.94 g/mol), dihydrate ($\text{Na}_2\text{HPO}_4 \cdot 2\text{H}_2\text{O}$, CAS 10028-24-7, 177.98 g/mol), heptahydrate ($\text{Na}_2\text{HPO}_4 \cdot 7\text{H}_2\text{O}$, CAS 7782-85-6, 268.03 g/mol), or dodecahydrate ($\text{Na}_2\text{HPO}_4 \cdot 12\text{H}_2\text{O}$, CAS 10039-32-4, 358.08 g/mol). Ex. 1022 at 20, Ex. 1023 at 20.

155. A disodium hydrogen phosphate buffer can be prepared by dissolving the dihydrate form of disodium hydrogen phosphate in water, which is commonly done for buffers of parenteral formulations. If given as a molar amount of disodium hydrogen phosphate, a person of ordinary skill could figure out how much to include and would know that the hydrates are interchangeable as the final formulation is aqueous. If given as a “mass” amount, a person of ordinary skill could use standard texts such as Remington’s 1990 (Ex. 1013 at 51-52) as a guide for how much to use, if not specified. Because phosphate buffers are so commonly used in parenteral formulations, it would have at least been obvious to use a disodium hydrogen phosphate dihydrate buffer, and a person of skill in the art would have expected a disodium hydrogen phosphate buffer to work as a buffering agent in the claimed formulation.

156. As discussed above, the formulations disclosed in Example 7 of Flink specifically use the dihydrate form of disodium hydrogen phosphate (“disodium hydrogenphosphate, dihydrate”) at a concentration of 1.42 mg/ml. Ex. 1004, 45–46.

Thus, a POSA would have at once envisioned that the disodium hydrogen phosphate disclosed in Flink included the dihydrate form. As such, Flink discloses the claimed disodium phosphate dihydrate buffer.

3. Flink disclosed the claimed isotonic agent

157. Claim 14 of Flink also disclosed “an isotonic agent” that is “present in a concentration from 1 mg/ml to 50 mg/ml.” Flink’s disclosure states that the isotonic agent is selected from a group “consisting of a salt (e.g. sodium chloride), a polyhydric alcohol (e.g. propyleneglycol, xylitol, mannitol, sorbitol or glycerol), a monosaccharide (e.g. glucose or maltose), a disaccharide [sic] (e.g. sucrose), an amino acid (e.g. L-glycine, L-histidine, arginine, lysine, isoleucine, aspartic acid, tryptophan, threonine), or polyethyleneglycol (e.g. PEG400).” Ex. 1004, 19:34-20:4. Because Flink expressly discloses propylene glycol as one of a small group of isotonic agents that would have been an acceptable isotonic agent at a concentration within the scope of claim 14, a person of ordinary skill would have at once envisioned using propylene glycol in the claimed formulation at a concentration between 1 to 50 mg/ml.

4. It would have been obvious to select propylene glycol

158. A person of ordinary skill would have been motivated to select propylene glycol from the list of isotonic agents disclosed by Flink. Propylene glycol was well known to be used for many purposes in pharmaceutical formulations,

including as a solvent, a co-solvent, a preservative, a humectant, a stabilizer, and a tonicity adjusting agent (i.e., an isotonic agent). Ex. 1007 at ¶[0014]; Ex. 1008 at 5; Ex. 1013 at 251; Ex. 1014 at 10:1-8; Ex. 1019 at 10:10-18, 13:11-17, 23:10-22; Ex. 1023 at 17; Ex. 1024 at 32; Ex. 1025 at 28:24-27; Ex. 1026 at 23-24, 26, Table 1; Ex. 1063 at 4:31-33; Ex. 1064 at 4:61-66; Ex. 1065 at 7:47-52. Propylene glycol's use as a tonicity adjusting agent was well documented in the prior art, having been specifically considered as such in Flink as well as many other patents and patent applications. *See, e.g.*, ¶¶85, 96, 102, 112, 110, 142, 143, 146 (Exs. 1004, 1005, 1007, 1014, 1025, 1063, 1064, 1065). As a polyhydric alcohol, propylene glycol is known to stabilize proteins in solution in varying concentrations from 1.0% to 10%, which falls in the claimed concentration range of 10 mg/ml to 100 mg/ml. Ex. 1026 at 26.

159. Thus, propylene glycol was well known by a person of ordinary skill to be a “widely used as a solvent, extractant, and preservative in a variety of parenteral and nonparenteral pharmaceutical formulations,” having the ability to “dissolve[] a wide variety of materials.” *Id.* A person of ordinary skill would have known that propylene glycol was often used in dosage forms where its liquid characteristics were helpful, including topical preparations, solutions, aerosol solutions, oral solutions, and parenterals. *Id.* Microbial contamination of parenteral formulations is particularly dangerous to patients due to the route of administration, and the person

of ordinary skill would be aware that propylene glycol is an antiseptic similar to ethanol, and only slightly less effective than ethanol against molds. *Id.* A person of ordinary skill would have been cautioned not to use propylene glycol at high concentrations, because doing so could cause pain or irritation during parenteral administration; however, such levels were unlikely to be reached because a mere “2% [by volume] aqueous solution is iso-osmotic with serum,” meaning that there was no reason to use propylene glycol in a parenteral formulation at concentrations having significant adverse effects. *Id.*

160. A POSA also would have known that propylene glycol has a relatively low safety risk in formulations. Propylene glycol was “generally regarded as a relatively nontoxic material” and was listed in the FDA Inactive Ingredients Guide for a number of routes of administration, including dental preparations, IM and IV injections, inhalations, ophthalmic, oral, otic, percutaneous, rectal, topical and vaginal preparations. Ex. 1022 at 18; Ex. 1023 at 18. For parenteral formulations, propylene glycol was an acceptable inactive ingredient in FDA-approved parenteral formulations. Ex. 1022 at 18; Ex. 1023 at 18. A person of ordinary skill would have been confident that selecting an FDA-approved isotonic would give a POSA a reasonable expectation that the agent would pose fewer regulatory hurdles toward clinical approval of the formulation.

161. Moreover, a person of ordinary skill would have been conscious of the number of excipients used in any pharmaceutical formulation, and would have minimized the number used to avoid increasing the possibility of undesirable interactions with a peptide drug or with a patient. Ex. 1005, 4; Ex. 1024 at 7.

162. Given its dependability and widespread use in pharmaceuticals, a person of ordinary skill would have known that propylene glycol would have served as a good choice as the tonicity agent in claim 14 of Flink, and also would have conferred other advantageous effects (e.g., stabilizing and antimicrobial effects) as well.

5. Calculating an appropriate concentration of propylene glycol was obvious

163. It was within the knowledge of one skilled in the art to calculate a concentration of propylene glycol that would confer an equivalent tonicity to the formulations disclosed in Example 7 of Flink.

164. A person of ordinary skill would understand that a parenteral formulation, especially if it is an injection, should be an isotonic formulation (or close to an isotonic formulation) to prevent pain and tissue damage upon administration. Ex. 1027 at 18, 22-23; Ex. 1013 at 308. An isotonic solution (as compared to plasma) is between approximately 275 mOsmol/L to just over 300 mOsmol/L. Ex. 1013 at 306. Once the final concentration of the primary components of a formulation (e.g., active ingredient, buffer system, and any stabilizing or

antimicrobial excipients or additives) have been determined, a person of ordinary skill would add a tonicity modifier to adjust the tonicity of the solution to be closer to an isotonic solution as discussed in the following paragraphs.

165. While there are many ways to calculate the tonicity of a solution to determine whether an isotonic is needed and how much, one of the more straightforward methods is to calculate the osmolarity, or “osmolar concentration” for each component of the final solution, the sum of which is roughly equivalent to the tonicity of the solution. *Id.* at 307. The formula to calculate the osmolar concentration is shown below as Formula 1:

$$\frac{\text{g/L}}{\text{mol wt}} \times 1000 = \text{mOsmol/L} \quad [\text{Formula 1}]$$

where “g/L” is the concentration of the agent, “mol wt” is the molecular weight of the agent, and the osmolar concentration for that agent is expressed in “mOsmol/L.” Ex. 1013, 307.

166. Calculating the osmotic concentration is a concept that is taught early in graduate school, if not earlier, and is an easy task for one of ordinary skill given the molecular weight of the agents and its contribution to the solutions tonicity. Standard reference books such as *Remington's* also show in detail how to perform these calculations. Ex. 1013 at 305-07. And, given that Flink discloses a couple of examples of formulations that include mannitol and glycerol as isotonic agents, the

calculation for determining how much propylene glycol to use in the formulation is simply a matter of determining the concentration of propylene glycol that would contribute the same osmolar concentration to the solution as mannitol or glycerol do. That calculation starts by determining the osmolar concentration for mannitol and glycerol in the Flink formulations, as shown below:

<u>For mannitol:</u>	<u>For glycerol:</u>
$\frac{36.9 \text{ g/L}}{182.17 \text{ g/mol}} \times 1000 = 202.56 \text{ mOsmol/L}$	$\frac{16.0 \text{ g/L}}{92.09 \text{ g/mol}} \times 1000 = 173.74 \text{ mOsmol/L}$
Concentration in Flink: 36.9 mg/ml (Ex. 1004, 27–35, 37–46)	Concentration in Flink: 16.0 mg/ml (Ex. 1004, 27–35, 37–46)
Molecular weight: 182.17 g/mol (Ex. 1022 at 12; Ex. 1023 at 12)	Molecular weight: 92.09 g/mol (Exs. 1022–1023 at 9)

167. Next, the amount of propylene glycol that would provide an equivalent osmolar concentration in the Flink formulations, one of ordinary skill would simply plug in the osmolar concentration for mannitol (202.56 mOsmol/L) or glycerol (173.72 mOsmol/L) and the molecular weight for propylene glycol (76.1 g/mol) into Formula 1, solving for the concentration of propylene glycol (PG) as shown in bold below:

<u>PG equivalent for mannitol:</u>	<u>PG equivalent for glycerol:</u>
$\frac{\text{PG g/L}}{76.09 \text{ g/mol}} \times 1000 = 202.56 \text{ mOsmol/L}$	$\frac{\text{PG g/L}}{76.09 \text{ g/mol}} \times 1000 = 173.74 \text{ mOsmol/L}$
propylene glycol = 15.41 mg/ml	propylene glycol = 13.22 mg/ml

168. Thus, one of ordinary skill would have understood that in order to produce formulations having an osmolarity equivalent to the Flink formulations containing mannitol or glycerol, propylene glycol would be added at a concentration of 15.41 mg/ml or 13.22 mg/ml, respectively. Accordingly, one of ordinary skill could have easily calculated a concentration of propylene glycol to adjust the tonicity of the formulation in an equivalent manner to the formulation disclosed by Flink. And, because the above concentrations fall within the claimed range of “about 1 mg/ml to about 100 mg/ml,” it would have been obvious to include propylene glycol at the claimed concentration. Remington’s also advises that for some complex and concentrated solutions it can be difficult to predict the osmotic strength *a priori*; however, for substitutions of uncomplex solutes in a formulation, Remington’s provides detailed instructions, examples, and tables for formulation of isosmotic and isotonic compositions. Ex. 1013 at 305-21. Remington’s 1990 and the U.S. Pharmacopeia & National Formulary 1990 also provide guidance and routine testing methods for formulation tonicity. Ex. 1013 at 311-313; Ex. 1068 at 130-31.

6. Flink disclosed the claimed pH

169. Claim 14 of Flink also expressly recited that “said formulation has a pH from 7.5 to 10.” Flink also disclosed several formulations having a pH between 7 and 10. *See, e.g.*, Ex. 1004, 27-35, 38-46. Thus, Flink disclosed the formulations having the claimed pH.

ii. Claims 2-4 Were Anticipated by or Would Have Been Obvious Over Flink

170. Claims 2-4 of the '833 patent depend from claim 1, and recite that the concentration of propylene glycol is from “about 1 mg/ml to about 50 mg/ml,” “about 5 mg/ml to about 25 mg/ml,” or “about 8 mg/ml to about 16 mg/ml,” respectively.

171. Claim 14 of Flink disclosed a concentration of the isotonic agent (propylene glycol) in a concentration “from 1mg/ml to 50mg/ml.” That disclosure is identical to that recited in claim 2, and encompasses the concentrations recited in claims 3 (“about 5 mg/ml to about 25 mg/ml”) and claim 4 (“about 8 mg/ml to about 16 mg/ml”). In addition, the disclosure of Flink also taught that the isotonic agent can be present in concentrations (i) from 8 mg/ml to 16 mg/ml, which is identical to the concentration recited in claim 4, or (ii) from 17 mg/ml to 50mg/ml, which falls within the range of claim 5. Accordingly, it is my opinion that claims 2-4 are anticipated or rendered obvious over Flink.

iii. Claims 5-7 Were Anticipated by or Would Have Been Obvious Over Flink

172. Claims 5-7 of the '833 patent depend from claim 1, and recite that the pH of the formulation is “about 7.0 to about 9.5,” “about 7.0 to about 8.3,” or “about 7.3 to about 8.3,” respectively.

173. By virtue of its dependency from claim 8, claim 14 of Flink disclosed a formulation having a pH between 7.5 and 10, which falls within the claimed range. Flink also disclosed several formulations that have a pH that falls within the claimed range. Ex. 1004, 27-35, 38-46 (Examples 1-7). Accordingly, it is my opinion that claims 5-7 are anticipated by or made obvious over Flink.

iv. Claims 8 and 9 Were Anticipated by or Would Have Been Obvious Over Flink

174. Claim 8 depends from claim 1 and recites that the formulation also includes a preservative. Claim 9 depends from claim 8, and further recites that the preservative is “present in a concentration from 0.1 mg/ml to 20 mg/ml.”

175. By virtue of its dependence on claims 11 and 12, claim 14 discloses a formulation having a preservative present at a concentration “from 0.1mg/ml to 20mg/ml.” Accordingly, it is my opinion that claims 8 and 9 are anticipated or made obvious over Flink.

v. Claim 10 Was Anticipated by or Would Have Been Obvious Over Flink

176. Claim 10 depends 1 and recites that the GLP-1 agonist is “selected from the group consisting of GLP-1(7-36)-amide, GLP-1(7-37), a GLP-1(7-36)-amide analogue, a GLP-1(7-37) analogue, or a derivative of any of these.”

177. By virtue of its dependence on claim 5, claim 14 of Flink disclosed that the GLP-1 compound is GLP-1(7-37) or an analog thereof. Accordingly, it is my opinion that claim 10 is anticipated or made obvious over Flink.

vi. Claim 11 Was Anticipated by or Would Have Been Obvious Over Flink

178. In my opinion, claim 21 of Flink anticipates or makes obvious claim 11 of the '833 patent. I understand that claim 21 of Flink is a dependent claim that requires all elements of the claims from which it depends. Here, claim 21 of Flink depends from several claims, including independent claim 5 and dependent claims 6, 8, 10, 11, 12, 13, and 14. A comparison of claim 11 of the '833 patent and claim 21 of Flink is shown below:

Claim 11 of '833 Patent	Claim 21 of Flink
11. The formulation according to claim 10, wherein said GLP-1 agonist is a derivative of <i>GLP-1(7-36)</i> or <i>GLP-1(7-37)</i> or a GLP-1(7-36)-amide analogue or a <i>GLP-1(7-37) analogue</i> , where said derivative has <i>a lysine residue and a lipophilic substituent attached with or without a spacer to the epsilon amino group of said lysine.</i>	21. The formulation according to any one of claims 1-20, wherein said GLP-1 compound is selected from a <i>GLP-1 (7-36), GLP-1 (7-37), or GLP-1 (7-38) analogue</i> having <i>a lysine residue, such as one lysine, wherein a lipophilic substituent optionally via a spacer is attached to the epsilon amino group of said lysine.</i>

179. I also note that Flink explains that “[d]erivatives of GLP-1 analogues are GLP-1 analogues which are chemically modified by introducing e.g. ester, alkyl or lipophilic functionalities on one or more amino acid residues of GLP-1 analogues.” Ex. 1004, 24:7-9. Thus, the GLP-1 analogue disclosed in claim 21 of

Flink is a derivative of a GLP-1 analogue at least by virtue of the lipophilic substituent attached to the epsilon amino group of said lysine. Accordingly, claim 11 of the '833 patent is anticipated or made obvious by Flink.

vii. Claim 12 Was Anticipated by or Would Have Been Obvious over Flink

180. In my opinion, claim 23 of Flink anticipates or makes obvious claim 12 of the '833 patent. I understand that claim 23 of Flink is a dependent claim that requires all elements of the claims from which it depends. Here, claim 23 of Flink depends from several claims, including independent claim 5 and dependent claims 6, 8, 10, 11, 12, 13, 14, and 21. A comparison of claim 12 of the '833 patent and claim 23 of Flink is shown below:

Claim 12 of '833 Patent	Claim 23 of Flink
12. The formulation according to claim 11, wherein said lipophilic substituent <i>has from 8 to 40 carbon atoms</i> .	23. The formulation according to any one of claims 1-22, wherein said lipophilic substituent <i>has from 8 to 40 carbon atoms</i> , preferably from 12 to 24, eg 14-18.

181. Accordingly, claim 12 of the '833 patent is anticipated or made obvious by Flink.

viii. Claim 13 Was Anticipated by or Would Have Been Obvious Over Flink

182. In my opinion, claim 24 of Flink anticipates or makes obvious claim 13 of the '833 patent. I understand that claim 24 of Flink is a dependent claim that

requires all elements of the claims from which it depends. Here, claim 24 of Flink depends from several claims, including independent claim 5 and dependent claims 6, 8, 10, 11, 12, 13, 14, 21, and 23. A comparison of claim 13 of the '833 patent and claim 24 of Flink is shown below:

Claim 13 of '833 Patent	Claim 24 of Flink
13. The formulation according to claim 12, wherein <i>said spacer is an amino acid</i> .	24. The formulation according to any one of claims 1-23, wherein said <i>spacer is present and is selected from an amino acid</i> , eg. Beta-Ala, L-Glu, aminobutyroyl.

183. Accordingly, claim 13 of the '833 patent is anticipated or made obvious by Flink.

ix. Claim 14 Was Anticipated by or Would Have Been Obvious Over Flink

184. In my opinion, claim 25 of Flink anticipates or makes obvious claim 14 of the '833 patent. I understand that claim 25 of Flink is a dependent claim that requires all elements of the claims from which it depends. Here, claim 25 of Flink depends from several claims, including independent claim 5 and dependent claims 6, 8, 10, 11, 12, 13, 14, 21, 23, and 24. A comparison of claim 14 of the '833 patent and claim 25 of Flink is shown below:

Claim 14 of '833 Patent	Claim 25 of Flink
14. The formulation according to claim 13, wherein said GLP-1 agonist is <i>Arg³⁴, Lys²⁶(N-ε-(γ-Glu(N-α-hexadecanoyl)))-GLP-1(7-37)</i> .	25. The formulation according to any one of claims 1-24, wherein said GLP-1 compound is <i>Arg³⁴, Lys²⁶(N-ε-(γ-</i>

	<i>Glu(N-α-hexadecanoyl)))-GLP-1 (7-37).</i>
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185. Accordingly, claim 14 of the '833 patent is anticipated or made obvious by Flink.

x. Claim 15 Was Anticipated by or Would Have Been Obvious Over Flink

186. In my opinion, claim 22 of Flink anticipates or makes obvious claim 15 of the '833 patent. I understand that claim 22 of Flink is a dependent claim that requires all elements of the claims from which it depends. Here, claim 22 of Flink depends from several claims, including independent claim 5 and dependent claims 6, 8, 10, 11, 12, 13, 14, and 21. A comparison of claim 15 of the '833 patent and claim 22 of Flink is shown below:

Claim 15 of '833 Patent	Claim 22 of Flink
15. The formulation according to claim 1, wherein said GLP-1 agonist is selected from the group consisting of Gly ⁸ -GLP-1(7-36)-amide, Gly ⁸ -GLP-1(7-37), Val ⁸ -GLP-1(7-36) amide, Val ⁸ -GLP-1(7-37), Val ⁸ Asp ²² -GLP-1(7-36)-amide, Val ⁸ Asp ²² -GLP-1(7-37), Val ⁸ Glu ²² -GLP-1(7-36)-amide, Val ⁸ Lys ²² -GLP-1(7-36)-amide, Val ⁸ Lys ²² -GLP-1(7-37), Val ⁸ Arg ²² -GLP-1(7-36)-amide, Val ⁸ Arg ²² -GLP-1(7-37), Val ⁸ His ²² -GLP-1(7-36)-amide, Val ⁸ His ²² -GLP-1(7-37), Arg³⁴GLP-1(7-37) , Arg ^{26,34} Lys ³⁶ GLP-1(7-36), Arg²⁶GLP-1(7-37) , and Gly ⁸ ,	22. The formulation according to claim 21, wherein said GLP-1(7-36), GLP-1(7-37), or GLP-1(7-38) analogue is selected from Arg³⁴GLP-1(7-37) , Arg ^{26,34} Lys ³⁶ GLP-1(7-36), Arg²⁶GLP-1(7-37) , or Gly ⁸ ,Arg ^{26,34} ,Glu ³⁷ ,Lys ³⁸ GLP-1(7-38).

Arg ^{26,34} Glu ³⁷ Lys ³⁸ GLP-1(7-38) and derivatives of any of these.	
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187. Accordingly, claim 15 of the '833 patent is anticipated or made obvious by Flink.

B. Claims 1-31 of the '833 Patent Would Have Been Obvious Over Flink in View of Betz

i. Claims 1-15 Would Have Been Obvious Over Flink in View of Betz

188. As shown below, Flink discloses a formulation that contains a GLP-1 agonist ("3 mg/ml [liraglutide]"), a disodium phosphate dihydrate buffer ("1.42 mg/ml disodium hydrogenphosphate, dihydrate"), and mannitol as an isotonic agent ("36.9 mg/ml mannitol") adjusted to pH 7.4. Ex. 1004 at 45 (Example 7).

Composition	pH	Temperature	Purity, Compound 1 (%) T = 12 weeks	Dimer formation, Compound 1 (%) T = 12 weeks
3 mg/ml Compound 1 1.42 mg/ml disodium hydrogenphosphate, dihydrate 5 mg/ml phenol 36.9 mg/ml mannitol	7.4	37°C	78.4	5.43

189. The only difference between Flink's formulation in Example 7 and the formulation recited in claim 1 of the '833 patent is that mannitol is used as an isotonic agent at a concentration of 36.9 mg/ml, instead of propylene glycol at a concentration between 1 and 100 mg/ml.

190. Betz disclosed protein formulations (in particular, for human growth hormone), designed to improve the storage stability and reduced or elimination of crystallization of the formulation during storage. Ex. 1005 at 5-8. Those improvements were attributed to the use of propylene glycol as both a stabilizer and an isotonic agent. *Id.* Betz also disclosed that replacing mannitol with propylene glycol resulted in an increase in stability of the formulation as measured by the time for crystallization to occur. Ex. 1005 at 18, Table 2. As show in Table 2 below, Betz disclosed propylene glycol at a concentration between 1 and 100 mg/ml in seven formulations as shown in Table 2 below (annotated):

Table 2: Composition of the final pharmaceutical formulations:

Formulation (in water for injection)	1	2	3	4	5
Human Growth Hormone	6,67 mg/ml	6,67 mg/ml	6,67 mg/ml	6,67 mg/ml	6,67 mg/ml
Na ₂ HPO ₄ x 7 H ₂ O °	0.49 mg/ml	0.49 mg/ml	0.49 mg/ml	0.49 mg/ml	0.49 mg/ml
NaH ₂ PO ₄ x 2 H ₂ O °	1.29 mg/ml	1.29 mg/ml	1.29 mg/ml	1.29 mg/ml	1.29 mg/ml
Benzyl Alcohol	9.0 mg/ml	9.0 mg/ml	9.0 mg/ml	9.0 mg/ml	9.0 mg/ml
Poloxamer 188	2.00 mg/ml	2.00 mg/ml	2.00 mg/ml	2.00 mg/ml	2.00 mg/ml
Mannitol	27.4mg/ml	25.0mg/ml	22.5 mg/ml	15.2 mg/ml	8.1 mg/ml
Glycine	---	---	---	---	---
1,2-Propylene Glycol	1.0 mg/ml	2.0 mg/ml	3.0 mg/ml	6.0 mg/ml	9.0 mg/ml
pH	6.2	6.2	6.2	6.2	6.2

° Including the phosphate from the hGH bulk solution.

Formulation	6	7	8
Human Growth Hormone	6,67 mg/ml	6,67 mg/ml	6,67 mg/ml
Na ₂ HPO ₄ x 7 H ₂ O °	0.49 mg/ml	0.89 mg/ml	0.89 mg/ml
NaH ₂ PO ₄ x 2 H ₂ O °	1.29 mg/ml	1.05 mg/ml	1.05 mg/ml
Benzyl Alcohol	9.0 mg/ml	9.0 mg/ml	9.0 mg/ml
Poloxamer 188	2.00 mg/ml	2.00 mg/ml	2.00 mg/ml
Mannitol	---	---	---
Glycine	---	---	7.5 mg/ml
1,2-Propylene Glycol	12.4 mg/ml	15 mg/ml	7.5 mg/ml
pH	6.2	6.2	6.2

° Including the phosphate from the hGH bulk solution.

Ex. 1005 at 17-18 (Table 2).

191. The Table 2 formulations, above, contain propylene glycol (shaded blue) at increasing concentrations of 1.0 mg/ml (Formulation 1), 2.0 mg/ml (Formulation 2), 3.0 mg/ml (Formulation 3), 6.0 mg/ml (Formulation 4), 9.0 mg/ml (Formulation 5), 12.4 mg/ml (Formulation 6), and 15 mg/ml (Formulation 7), all falling within the scope of claim 1. Thus, each limitation of claim 1 is explicitly disclosed by Flink in combination with Betz.

192. Some of the Betz formulations also contain mannitol. Ex. 1005 at 17-18 (Formulations 1–5). As the propylene glycol concentration was increased in the Betz formulations, the concentration of mannitol was decreased until propylene glycol wholly replaced mannitol. *Id.* (Formulations 6–7). Formulations 1-6 all have essentially the same osmolality, about 163 ± 1 mOsmol/L, from the combination of mannitol and propylene glycol, or from propylene glycol alone.⁴ Thus, Betz also disclosed replacing mannitol with propylene glycol.

193. For the following reasons, it is my opinion that a person of ordinary skill would have been motivated to modify the formulations of Flink to incorporate propylene glycol as an isotonic agent in view of Betz.

1. The common problem of peptide instability in formulations

194. First, a person of ordinary skill would have understood that protein instability was—and still is—a well-known problem in the development of peptide drug formulations. Ex. 1013 at 128-29 (“The formulation of a stable product is of

⁴ The osmolality contributed from mannitol and propylene glycol in each formulation was calculated using the formulas in Section 9.5 (¶¶163-168 and Formula 1). The results for Formulations 1-6, respectively, were 163.5 mOsmol/L, 163.5 mOsmol/L, 162.9 mOsmol/L, 162.3 mOsmol/L, 162.7 mOsmol/L and 162.9 mOsmol/L. The contribution to osmolality from human growth hormone, phosphate buffer components, benzyl alcohol, and poloxamer 188 were not included in the comparative calculations of osmolality since their concentrations are the same in Formulations 1-6.

paramount importance.”); Ex. 1024 at 4-5; Ex. 1008 at 1. Like any other peptide drug, native GLP-1 and GLP-1 agonists were known to have stability issues, including solubility and aggregation issues in solution. Ex. 1004 at 3:22-24; Ex. 1021 at 3-4; Ex. 1046 at 2; Ex. 1059, 1. Those issues continue to be a problem today. *See generally* Ex. 1066. As such, a person of ordinary skill would have looked for resources that offered suggestions for improving the stability of any peptide or protein in solution. Both Flink and Betz fit that bill.

195. In Flink, GLP-1 agonist formulations with enhanced stability were disclosed. For example, formulations for liraglutide were shown to exhibit improved stability as compared to formulations containing native GLP-1. Ex. 1004 at 38. In another example, Flink disclosed that certain stabilizers (imidazole, histidine, and arginine) significantly improved the chemical stability of liraglutide during long-term storage. Ex. *Id.* at 45–46. Betz also addressed the “long appreciated problem with aqueous liquid formulations of pharmaceutical proteins, *not just hGH*, is that of instability during storage over a period of time.” Ex. 1005 at 3 (emphasis added).

196. When designing a protein or peptide formulation, a person of ordinary skill would have routinely evaluated several factors to account for potential stability issues, including whether there are any excipients that could be used as stabilizers. Ex. 1026 at 7-8, 23. Thus, a person of ordinary skill concerned with developing formulations for improving stability of GLP-1 agonists—or any peptide—would

look to references like Betz. Betz would have been useful for its teaching of known excipients, like propylene glycol, to reduce precipitation or crystallization and improve long-term stability and storage—problems that were not limited to any one peptide. Ex. 1005 at 4-5; Ex. 1019 at 13, 23-24.

2. Flink taught that mannitol should not be used in formulations having a pH of 7.4

197. A POSA would have been motivated to replace mannitol in formulations having a pH of 7.4. Flink taught GLP-1 agonist formulations wherein “if an isotonic agent is present and pH is 7.4 then mannitol or NaCl is not the isotonic agent.” Ex. 1004 at 5:17-23. Given that instruction, a person of ordinary skill would have had a reason to replace some or all of the mannitol contained in the first Example 7 formulation (Ex. 1004 at 45) with an alternative isotonic agent. Propylene glycol would have been at the top of a POSA’s mind for the reasons set forth above in ¶¶68-80, 157-162. Additionally, Betz taught that propylene glycol “provid[es] stability to the pharmaceutical formulation and, simultaneously, it contributes to the desired tonicity of the formulation.” Ex. 1005 at 6. Betz further taught that while an additional isotonic agent—like mannitol—may be added, if necessary, propylene glycol, together with other excipients, is sufficient to provide the desired tonicity of a peptide formulation “without the need of an additional tonicity-adjusting agent to be present, thereby keeping the overall number of excipients to be used to a minimum.” *Id.* at 7. And because Betz suggests that replacing mannitol with

propylene glycol—one of the isotonic agents expressly named as an alternative in Flink—it would have been obvious to a person of ordinary skill to simply substitute mannitol with propylene glycol in the first Example 7 formulation of Flink.

198. Thus, given that both Flink and Betz both taught what POSAs already knew—that propylene glycol was an appropriate isotonic agent (*see* ¶¶157, 197)—and that Betz taught that propylene glycol was a superior stabilizer to mannitol (*see* ¶190), a POSA would have substituted propylene glycol for the mannitol contained in Formula 7 of Flink (in whole or in part). It would also have been obvious to provide a final concentration of propylene glycol based on that provided by Betz, or by calculating the amount of propylene glycol needed as discussed above in ¶¶163-168.

3. It would have been obvious to solve the problem of precipitation with propylene glycol

199. Crystallization and precipitation of peptides due to physical instabilities like denaturation and aggregation is a well-known problem addressed by Betz. Ex. 1005, 3. Betz disclosed seven formulations that were studied to determine their propensity to crystallize. Ex. 1005, 17-18. When stored at temperatures of 15°C and 25°C, Formulations 1 to 4—in which the mannitol concentration is greater than the concentration of propylene glycol—exhibited crystallization at 4 weeks. Formulations 5 to 7—in which the concentration of propylene glycol is greater than that of mannitol (Formulation 5) or in which propylene glycol completely replaced

mannitol (Formulations 6 and 7)—did not exhibit crystallization until at least 7 weeks.

200. Other solutes in a pharmaceutical formulation were also known have problems with crystallization and precipitation, including mannitol. Mannitol had a propensity to precipitate out of solution in parenteral formulations at concentrations above 18% w/v and when in contact with plastic. See ¶¶76-77.

201. Mannitol's proclivity to precipitate had also been recognized to cause problems with respect to its use as an excipient in peptide formulations. For example, it was known that mannitol tends to crystallize during freeze-drying, and thus may not be the best choice as a stabilizer. Ex. 1024, 32. Patent Owner also recognized "that mannitol causes problems during the production of peptide formulations as it crystallizes resulting in deposits in the production equipment and in the final product" and "the presence of mannitol results in clogging of injection devices." Ex. 1001 at 1:30-45.

202. The problem of precipitation and leaving deposits on production equipment and injection needles is not surprising given that mannitol is naturally a solid under standard conditions (e.g., at room temperature and at atmospheric pressure). *See, e.g.*, Ex. 1022 at 12 (showing mannitol's melting point as 166-168°C); Ex. 1023 at 13 (same); *see also* ¶¶76-78 above.

203. In contrast, a POSA would have known that propylene glycol is naturally a liquid solvent under standard conditions (e.g., at room temperature and atmospheric pressure). *See, e.g.*, Ex. 1022 at 17 (showing propylene glycol's melting point as -59°C), Ex. 1023 at 17 (same). Although certain liquids including water can readily evaporate at ambient conditions, leaving their non-volatile contents behind, one of ordinary skill would be aware that propylene glycol—a liquid—has a “lack of volatility” and would not leave deposits behind. *Id.* In addition, a well-known use of propylene glycol was as a humectant, an agent that is hygroscopic and keeps substances moist. Ex. 1022 at 17; Ex. 1023 at 17. Propylene glycol is commonly used in topical formulations used to prevent drying out, and in emulsions to prevent evaporation of formulation water from product container when the closure is removed. Ex. 1061 at 48; Ex. 1013 at 246, 251.

204. In view of the foregoing, it is my opinion that replacing mannitol with propylene glycol would produce predictable results and thus claim 1 is made obvious by Flink in view of Betz. Further, claims 2-15 are also made obvious by Flink in view of Betz for the same reasons set forth above in ¶¶170-187.

ii. Claim 16 Would Have Been Obvious Over Flink in View of Betz

205. Claim 16 is directed to a method of preparing a GLP-1 agonist formulation suitable for an injection device. Flink teaches that the formulations described therein are suitable for parenteral administration “performed by

subcutaneous, intramuscular or intravenous injection by means of a syringe, optionally a pen-like syringe.” Ex. 1004 at 17:23–25.

206. Like claim 1, claim 16 of the ’833 patent recites a formulation having a pH of from about 7.0 to about 10.0 and containing a GLP-1 agonist, a disodium phosphate dihydrate buffer and propylene glycol in a final concentration of from about 1 mg/ml to about 100 mg/ml. Thus, for the same reasons that the formulation recited in claim 1 is anticipated or obvious stated above, Flink anticipates or makes obvious the formulation recited in claim 16.

207. Claim 16 also recites that the formulation includes a preservative. Thus, for the same reasons that the formulation recited in claim 8 is anticipated or obvious stated above, Flink anticipates or makes obvious the preservative recited in claim 16.

208. Claim 16 further recites steps of mixing the GLP-1 agonist, the propylene glycol, the buffer, and the preservative together by:

- preparing a first solution by dissolving preservative, propylene glycol, and buffer in water,
- preparing a second solution by dissolving preservative propylene glycol and buffer in water,
- mixing the first and second solutions; and
- adjusting the pH of the mixture in (c) to a pH of about 7.0 to about 10.0.

209. Those steps are disclosed by Betz. Betz discloses pharmaceutical formulations that were prepared by adding a “bulk hGH solution” to a “triple concentrated excipient solution.” Ex. 1005 at 16-17. The triple concentrated excipient solution was prepared in a phosphate buffer solution and contained propylene glycol and a preservative (benzyl alcohol). *Id.* (Table 2). After the excipient mixture is mixed with the bulk hGH solution, the pH is adjusted to the desired value. *Id.* at 17. A person of ordinary skill would have prepared the GLP-1 formulations disclosed by Flink following the conventional formulation techniques demonstrated in Betz.

iii. Claims 17-19 Would Have Been Obvious Over Flink in View of Betz

210. Claims 17, 18, and 19 of the '833 patent depend from claim 16 and recite that the concentration of propylene glycol is from about 1 mg/ml to about 50 mg/ml, about 5 mg/ml to about 25 mg/ml, or about 8mg/ml to about 16 mg/ml, respectively. For the same reasons that the formulation recited in claims 2, 3, and 4 are anticipated or obvious stated above, Flink anticipates or makes obvious the formulation recited in claims 17, 18, and 19, respectively.

iv. Claims 20-22 Would Have Been Obvious Over Flink in View of Betz

211. 211. Claims 20, 21, and 22 of the '833 patent depend from claim 16 and recite that the pH of the formulation is about 7.0 to about 9.5, 7.0 to about 8.0, or 7.2

to about 8.0, respectively. Flink anticipated claims 5, 6, and 7 because Flink taught that the formulation has a pH in the range from 7.0 to 9.5, from 7.0 to 8.0, and from 7.5 to 8.0, respectively. Ex. 1004 at 18:20-26. Further, Flink taught several specific formulations that have a pH that falls within the claimed ranges, thereby anticipating or rendering obvious claims 5, 6, and 7. *See* Ex. 1004 at 27-35, 38-46 (Examples 1-7).

v. Claims 23, 26, and 29 Would Have Been Obvious Over Flink in View of Betz

212. Independent claims 23, 26, and 29 recite methods for reducing deposits on production equipment (claim 23) and in the final product (claim 26) and for reducing clogging of injection devices (claim 29). Each of claims 23, 26, and 29 recite replacing an isotonicity agent in an existing formulation that includes a disodium phosphate dihydrate buffer with propylene glycol at a concentration of between 1-100 mg/ml. For all of the reasons set for the above, one skilled in the art would have replaced mannitol in the formulations disclosed in Flink with propylene glycol in view of Flink and Betz. Further, as discussed above, one skilled in the art would have understood that replacing mannitol with propylene glycol would have reduced deposits and clogging as a result of inherent properties of propylene glycol as a liquid solvent as opposed to mannitol as a solid solute.

213. Further, one skilled in the art would have provided propylene glycol in a final concentration of from about 1 mg/ml to about 100 mg/ml for the reasons set forth above with respect to claim 1 (see ¶¶ 157-162). Thus, Flink and Betz renders obvious the methods recited in claims 23, 26, and 29.

vi. Claims 24, 27, and 30 Would Have Been Obvious Over Flink in View of Betz

214. Claims 24, 27, and 30 depend from claims 23, 26, and 29, respectively, and further recite specific experiments for measuring the reduction of deposits or clogging of injection devices. The claimed simulated filling experiment of claim 24, the reduction in the number of vials and/or cartridges that must be discarded due to deposits relative of claim 27, and the simulated use study of claim 30 would be obvious as part of routine finished product testing to ensure quality and stability. For example, one skilled in the art would have performed studies of finished product to include evaluation of characteristics including color changes, clarity, pH, moisture transfer, extractables, tonicity, binding, adsorption, potency, stopper appearance, aggregation, particulates, and container closure integrity, and for a multidose formulation test for residual preservative(s). Ex. 1026 at 36-39; Ex. 1013 at 280-95, 322-27, 376-78; Ex. 1068 at 3-158. In particular, one of ordinary skill would have known to:

- test for deposits on production equipment to determine whether any adsorption or surface precipitation of the formulation would have taken

place while in contact with the equipment (Ex. 1024 at 69-70, 120-21; Ex. 1075 at 13-15, 17-18; Ex. 1072 at 1);

- evaluate the visual appearance of the device (e.g., an injection device), vial and/or cartridge for the formation of particulates under storage conditions in product samples maintained in inverted or horizontal positions (Ex. 1024 at 63-68, including Table XVI; Ex. 1070 at 18; Ex. 1075 at 17, 19; Ex. 1068 at 131-33);
- test whether a multiple-dose application (e.g., vial of injectable formulation or an injection device) is capable of withstanding repeated insertions and withdrawals (*Id.* at 53-54, 65; Ex. 1070 at 17; Ex. 1073 at 1-4 (study of injection pen needle performance with vials and cartridges)); and
- discard vials or cartridges that have deposits or precipitation, and to keep track of the number discarded for quality control purposes (Ex. 1024 at 98-99; Ex. 1069 at 4-8);

215. Injection devices like injector pens are multiple-dose devices with known issues that must resolved using standard tests like these, because the device is often stored and used at room temperature, and because the device is used repeatedly over time and there needs to be assurance that the dose accuracy and

delivery does not change over time. Ex. 1024 at 53-54; Ex. 1070 at 17; Ex. 1073 at 1; Ex. 1071 at 1-3; Ex. 1074 at 1, 4-5.

216. Further, a person of ordinary skill would also know that precipitation can occur at any stage of manufacturing, including “in membrane filters, filtration equipment, pumps, and tubing” and that taking steps like adding stabilizing ingredients can reduce or avoid precipitation. Ex. 1026 at 17-18. Testing whether surface precipitation or adsorption occurred is routine and testing whether a particular formulation has the propensity to precipitate or become adsorbed onto the production equipment could have been performed by exposing a small quantity of the formulation to a scaled-down version of the production equipment for a period of time to detect whether adsorption of any component of the formulation occurs. Ex. 1024 at 120-21; Ex. 1075 at 15-17; Ex. 1072 at 1.

217. As such, one skilled in the art would have already been testing and evaluating the final products for problems and would have performed those tests to ensure the final products are safe and effective. Thus, it is my opinion that claims 24, 27, and 30 are obvious.

vii. Claims 25, 28, and 31 Would Have Been Obvious Over Flink in View of Betz

218. Claims 25, 28, and 31 depend from claims 23, 26, and 29, respectively, and further recite the specific isotonicity agent to be replaced by propylene glycol. One of the agents that can be replaced according to the claims is selected from a

group that includes mannitol. For all the reasons set forth above and with respect to claims 23, 26, and 29, Flink and Betz make obvious replacing mannitol with propylene glycol.

10. NO SECONDARY CONSIDERATIONS OVERCOME *PRIMA FACIE* OBVIOUSNESS OF THE CLAIMED INVENTIONS

A. The Methods Recited in the '833 Patent Produce No Unexpected Results

219. The claims of the '833 patent recite (i) methods for preparing GLP-1 agonist formulations including propylene glycol in a final concentration from about 1 mg/ml to about 100 mg/ml (claims 16-22) and (ii) methods related to the results of using such formulations, as compared to formulations containing isotonic agents other than propylene glycol (claims 23-31). As discussed above, *see* Sections 9.a-9.b, prior art like Flink—alone or in combination with Betz—disclosed, contemplated, and/or claimed formulations containing the claimed concentration of propylene glycol. The patent disclosed no unexpected results from the claimed formulation.

220. Regarding the methods directed to preparing GLP-1 agonist formulations, the steps for mixing the components in two separate solutions and combining them to generate the final formulation are merely routine steps a POSA would consider for formulating the final solution. Ex. 1001 at 16:5-30. The substitution of mannitol with propylene glycol for tonicity adjustment, in a

formulation of a polypeptide to reduce or prevent crystallization, was already taught in Betz. Ex. 1005 at 17-18 (Table 2); see also ¶¶176, 179. The remaining limitations recited in claims 16-22 relate to the formulation features recited in claims 1-15, which Flink disclosed alone or in combination with Betz. Thus, the methods for preparing the GLP-1 agonist formulations are not unexpected results because the administered formulation was disclosed and/or claimed in the prior art.

221. In addition, the claimed methods related to reducing deposits or clogging (claims 23-31) could not have been unexpected because they are simply the inherent results of using a formulation containing propylene glycol, rather than mannitol or another isotonic agent. *Supra*, Sections 9.b.v-vii. In addition, the inclusion of propylene glycol in formulations to prevent loss of water, which would prevent formation of dried residues, was well known and taught in standard formulation texts. Ex. 1061 at 48; Ex. 1013 at 246, 251; *see also supra* Section 8.c.xv.

B. There Was No Long-Felt But Unmet Need

222. Patent Owner may allege satisfaction of a long-felt but unmet need for GLP-1 agonist formulations that reduce deposits and clogging. But, any long-felt but unmet need was satisfied by the formulations disclosed in Flink alone or in combination with Betz.

C. There Was No Industry Skepticism

223. Nor will Patent Owners be able to establish industry skepticism. The claimed formulation was expressly disclosed and/or contemplated by Flink, so any skepticism would have to be directed to the specific results of using the formulation, which are inherent. Thus, even if Patent Owners could show that others considered alternative formulations to be superior to the GLP-1 agonist formulations disclosed in Flink, it would not change the fact that the formulation was known in the prior art.

D. Copying By Generic Drug Makers Is Irrelevant

224. Patent Owner may argue that Petitioner and other generic drug companies seek to copy the invention. But I understand from counsel that “evidence of copying in the [generic drug] context is not probative of nonobviousness.” *Bayer Healthcare Pharm., Inc. v. Watson Pharm., Inc.*, 713 F.3d 1369, 1377 (Fed. Cir. 2013) (citation omitted). Given that understanding, any work by Pfizer to develop a product like the inventions claimed in the ’833 patent is not evidence of nonobviousness.

E. A Blocking Patent Existed at the Time of the Claimed Invention

225. In addition to the reasons described above, any claimed secondary considerations, including any claims of commercial success, would not be evidence of nonobviousness of the claims of the ’833 patent because other companies were

prevented from making the claimed pharmaceutical composition by a patent blocking such development, as discussed below.

226. I understand from counsel that a party's patent is a "blocking patent" when it effectively blocks others from making, using, or selling a given product or using a given method. I further understand from counsel that a court may find that evidence of secondary considerations of nonobviousness, in the presence of a blocking patent, may provide little or no probative value on whether a claimed invention is nonobvious.

227. Here, U.S. Patent No. 6,268,343 ("343 patent"), entitled "Derivatives of GLP-1 Analogs," claims liraglutide. *See* Ex. 1006, 268:24-25 (claim 23). According to the FDA's Orange Book, in which a company may list one or more patents alleged to cover the company's pharmaceutical product, the '343 patent is listed as allegedly covering Victoza. The '343 patent was filed in 1999, claiming priority to 1997, and issued in 2001. Thus, the '343 patent issued long before the earliest filing date (2003) to which the '833 patent may claim priority. According to the FDA, the '343 Patent is expected to expire in August 2022, with pediatric exclusivity extending to February 2023.

228. The '343 patent is a blocking patent for the invention claimed in the '833 patent because the '343 patent claims a compound (liraglutide) that is a GLP-1 agonist, as claimed in the broadest claims of the '833 patent. This is a disincentive

for potential competitors to research, develop, and commercialize liraglutide in a dosage form that could fall within the '833 patent's claimed subject matter; the competitors would not be able to bring such a product to market. Thus, at least any alleged evidence of commercial success, and other secondary considerations, carries less or no probative weight in this case.

229. Because Patent Owner has not yet made its position known on any secondary considerations, I reserve the right to address any secondary considerations put forth by Patent Owner in any later response to this declaration or the petition it accompanies.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine, imprisonment, or both, under Section 1001 of Title 18 of the United States Code.

Date: July 22, 2020



Laird Forrest, Ph.D.

EXHIBIT A

Laird Forrest, Ph.D.

Professor
Department of Pharmaceutical Chemistry, School of Pharmacy
University of Kansas, Lawrence, KS 66047

Education

Post-doctoral fellow, Pharmaceutical Sciences, University of Wisconsin, Madison, WI	2006
Ph.D. Chemical and Biomolecular Engineering, University of Illinois, Urbana, IL	2003
M.S. Chemical Engineering, University of Illinois, Urbana, IL	2001
B.S. Chemical Engineering, Auburn University, Auburn, AL (<i>Summa Cum Laude</i>)	1998

Academic Professional Experience

Full Professor, Department of Pharmaceutical Chemistry, University of Kansas, 3/2017-present (primary appointment)
Adjunct/Courtesy Appointments:
Bioengineering Center, University of Kansas, 6/2011-present
Department of Medicinal Chemistry (courtesy), University of Kansas, 12/2015-3/2018
Department of Chemistry (courtesy), University of Kansas, 11/2013-11/2016
Associate Professor, Department of Pharmaceutical Chemistry, University of Kansas, 8/2013-2/2017
Research Associate Professor (volunteer), Department of Internal Medicine, Division of Dermatology, University of Kansas Medical Center, 6/2011-6/2015 (listed appointments were at Asst. Prof. level prior to 8/2013)
Assistant Professor, Department of Pharmaceutical Chemistry, University of Kansas, 1/2007-8/2013
Adjunct Assistant Professor, Dept. of Pharmaceutical Sciences, Washington State University, Pullman, 11/2006-11/2013
Postdoctoral Fellow, Division of Pharmaceutical Sciences, University of Wisconsin, Madison, 2004-2006
Graduate Research Assistant, Department of Chemical Engineering, UIUC, 1998-2003

Other Professional Experience

Hylapharm LLC, co-founder, 2011-present
HylaPharm is developing injected and locally administered anti-cancer therapeutics.
Aerobyx LLC, co-founder, Chief Operating Officer, 2017-present
Aerobyx is developing bioenergetic medicines for neurodegenerative diseases.
Vesarex LLC, co-founder, Chief Operating Officer, 2018-present
Veserax is developing devices and treatments for vascular disease.
Exogenesis Corporation, Member of Scientific and Medical Advisory Board, 2009-present
Exogenesis is developing and commercializing nanoscale surface modification for improving the safety and efficacy of implantable medical devices
Patent Writer, Beem Patent Law Firm, Chicago, IL, 2003-2004
Drafted and assisted in prosecution of patent applications, provided in-house scientific expert support.
Software Engineer/Consultant, Packaging Corporation of America (multiple sites), 1994-present
Developed and managed custom software for analysis of real-time manufacturing quality control systems and integration with product tracking in business data systems.
Expert witness (prior 6 years)

1. Medac Pharma, Inc., et. al. v. Antares Pharma Inc., et al., Civ. No. 1:14-cv-01498-JBB (D. NJ) (2014) (engaged by Antares, did not testify)
2. Par Pharmaceutical, Inc., et al. v. Breckenridge Pharmaceutical, Inc., et al., Civ. No. 1:15-cv-00486-SLR (D. DE) (2015) (engaged by Par, did not testify)
3. Merck Sharp & Dohme Corp. v. Savior Lifetec Corp., Civ. No. 5:15-cv-415 (E.D.N.C) (2016) (engaged by Savior, testified)
4. Mylan Pharmaceuticals Inc. v. Astrazeneca AB; PTAB IPR2016-01326; PTAB IPR2016-01325; PTAB IPR2016-01324; PTAB IPR2016-01316 (Inter Partes Review filed before the Patent Trial and Appeal Board, 2016) (engaged by Mylan, did not testify)
5. Horizon Pharma, Inc., Horizon Pharma USA, Inc. and Pozen Inc. v. Mylan Pharmaceuticals Inc., Mylan Laboratories Limited, and Mylan Inc; Civ. No. 3:15-cv-03327-MLC-DEA, 3:16-cv-04921 (D. NJ); *joint* Horizon Pharm, Inc., Horizon Pharma USA, Inc., and Pozen Inc. v. Dr. Reddy's Laboratories, Inc. and Dr. Reddy's Laboratories; Civ. No. 3:15-cv-03324 (D. NJ), 3:16-cv-04918 (D. NJ), 3:16-cv-09035 (D.NJ); *joint* Horizon Pharm, Inc., Horizon Pharma USA, Inc., and Pozen Inc. v. Lupin Ltd. and Lupin Pharmaceuticals Inc.; Civ. No. 3:15-cv-03326 (D. NJ), 3:16-cv-04920 (D.NJ) (2017) (engaged by Mylan, DRL and Lupin, testified)
6. Halozyme, Inc. v. Joseph Matal (on behalf of USPTO). Civ. No. 1:16-cv-1580 (E.D. Va) (2017) (engaged by USPTO, testified).

7. Bracco Diagnostics Inc. v. Maia Pharmaceuticals, Inc. Civ. No. 3:17-cv-13151 (D. NJ) (2018) (engaged by Bracco, testified).

Awards and Honors

Baxendale Innovation Award, 2016
University of Kansas Leading Light award, 2014
Japan Society for Promotion of Science (JSPS) Visiting Scholar Fellow, 2010
American Cancer Society Research Scholar, 2008-2012
American Association of Colleges of Pharmacy, New Investigators Award, 2007
PhRMA Foundation Postdoctoral Fellow, 2006
Controlled Release Society Annual Meeting, Glasgow, Scotland.
Student poster abstract award (unable to attend), 2003
American Institute of Chemical Engineers Annual Conference, Reno, NV
Pharmaceutical and Biotechnology Program Student Paper Award, 2001
Carriers in Gene Therapy Session Speaker Award, 2001
Auburn P&P Foundation Scholarship; Tenneco Engineering Scholarship, 1994-1998

Teaching

Full courses

Biopharmaceutics and Drug Delivery (PharmD professional course), PHCH626, yearly Spring 2011-present, *Course coordinator and instructor*
Drug Delivery (graduate course), PHCH715, CP&E 715; yearly Spring 2016-present, *Course instructor*
Introduction of Clinical Chemistry (PharmD professional course) PHCH667; Spring 2007-2010, *Course coordinator and instructor*
Pharmaceutical Equilibria (graduate course), PHCH862/3; yearly Fall 2008-Fall 2017, *Course coordinator and instructor*
Physical Chemistry of Pharmaceutical Solutions, Solids and Surfaces (graduate course), PHCH862/3, yearly Fall 2018-present, *Course instructor*

Short courses

Short course on Drug Delivery (15 lectures / 1 credit hr), *Course developer and instructor*
Shandong University, China (July 2009)
Tsukuba University, Japan (July 2009)
Short course on Drug Formulation and Basic Pharmacokinetics (15 lecture hours/1 credit hr), *Couse developer and instructor*
Tsukuba University, Japan (August 2010)

Partial courses and invited course lectures

Drug Delivery PHCH 715; Fall 2007, 2009, 2011, 2013, 2015 (became instructor in full course Spring 2016)
Emerging Trends in Pharmaceutical Chemistry PHCH 511; Fall 2007, Fall 2008 – present, every even year
Introduction to Nanotechnology, C&PE 656; Spring/Fall 2009-2014 (guest lecturer)
Sigma Xi Continuing Education series, KUMC Fall 2007 (guest lecturer).

Patents and Applications

1. Rowe PSN, Martin A, David NV, Forrest ML, Moulder KR, Cai S, DJ Aires. "Compounds and methods for increasing hair growth." US Patent 10,350,263 (granted 7/16/2019)
2. Forrest ML Hunt J, Aires DH, Cai S, Lu R, Groer C, Moulder R, Kleindl P. "Investigations of the phenyl ring of imidazoquinolines." US Provisional 62/835,408 (filed 4/17/2019).
3. Swerdlow R, Forrest ML, Michaelis E, Hunt J, Wilkins H. "Bioenergetically active esters for health and disease." US Nonprovisional Application (international app. PCT/US19/53901) (filed 9/30/2019).
4. Buchman SR, Cohen M, Donneys A, Nelson N, Forrest ML, Zhang T, Yang Q. "Devices, compositions and related Methods for accelerating and enhancing bone repair." (filed, 12/17/2015), WO2017/106744, PCT/US2016/067320
5. Forrest ML, Cai S, Zhang T, Senadheera SPSN, Groer C, Aires D, "Drug delivery compositions and methods." US Pat. Prov. Application 62/274,508 (filed 1/4/2016), non-provisional patent filed 1/3/2017, CIP 16/067,630 filed 7/2/2018
6. Forrest ML, Kleindl P, Senadheera SPSN, "Immunosuppressive compositions" US Pat. Prov. Application (filed 3/3/2016).
7. Forrest ML, Cai S, Zhang T, Senadheera SPSN, Duan S, Groer C, Aires D, Zhao Y, "Targeted mTOR Inhibitor." US Pat. Non-provisional Application 15/052,302 (filed 2/24/2016) (priority to Prov. Application 62/120,215, 2/24/2015).
8. Kwon, G.S. and M.L. Forrest, "Micelle composition of polymer and passenger drug." US Pat 9,107,814 (granted 8/18/2015).

9. Forrest ML, Cai S, Duan S, Zhang T, Yang Q, "Drug and imaging agent delivery compositions and methods" US Pat. 8,802,235. (granted 4/4/2014)
10. Rowe P, Forrest ML, Moulder R, Cai S, Martin A, Aires D. "Preparations for enhancement of hair growth" US Pat. 10,213,479 (granted 2/26/2019).
11. Rowe P, Forrest ML, Moulder R, Cai S, Martin A, Aires D. "Preparations for enhancement of hair growth" US Divisional application (filed 2/13/2019) (priority to PCT/US2015/012691, filed 1/23/2015 16/275,069)
12. Forrest ML, Cohen MS, Cai S, "Intralymphatic chemotherapy drug carriers" US Pat. 8,088,412 (granted 1/3/2012) (International filings 1/30/2009)
13. Forrest ML, Cohen MS, Cai S, "Intralymphatic chemotherapy drug carriers" Korean Patent 10-1224711 (granted 2/18/2013)
14. Forrest ML, Cohen MS, Cai S, "Intralymphatic chemotherapy drug carriers" Japanese Patent 5,302,340 (granted 6/28/2013)
15. Forrest ML, Cohen MS, Cai S, "Intralymphatic chemotherapy drug carriers" Chinese Patent 101965201 B (granted 10/23/2013)
16. Forrest ML, Cohen MS, Cai S, "Intralymphatic chemotherapy drug carriers" Canada Application 2,713,813
17. Forrest ML, Cohen MS, Cai S, "Intralymphatic chemotherapy drug carriers" CIP 13/341,282 (filed 1/3/2012)
18. Forrest ML, Cohen MS, Cai S, "Intralymphatic chemotherapy drug carriers" France Brevet No. 2242514 (granted 9/30/2015)
19. Forrest ML, Cohen MS, Cai S, "Intralymphatic chemotherapy drug carriers" Germany DBP No. 60 2009 033 907 (granted 9/30/2015)
20. Forrest ML, Cohen MS, Cai S, "Intralymphatic chemotherapy drug carriers" U.K. Patent No. 2242514 (granted 9/30/2015)
21. Kwon, G.S., and M.L. Forrest, "Micelle composition of polymer and passenger drug." US Pat. 8,173,167 (granted 5/11/12)
22. Kwon, G.S., M.L. Forrest, and N.M. Davies. "Micelle encapsulation of therapeutic agents." US App 20100203114

Peer Reviewed Publications (chronological order)

List also available as:

<http://www.ncbi.nlm.nih.gov/myncbi/browse/collection/41384976/?sort=date&direction=ascending>

1. Forrest, M.L., D.W. Pack. "On the Kinetics of Polyplex Endocytic Trafficking: Implications for Gene Delivery Vector Design." *Mol. Ther.* 6: 57-66 (2002). PMID: 12095304
2. Forrest, M.L., J.T. Koerber, and D.W. Pack. "A Degradable Polyethylenimine Derivative with Low Toxicity for Highly Efficient Gene Delivery." *Bioconjug. Chem.* 14: 934-940 (2003). PMID: 13129396
3. Forrest, M.L., G.E. Meister, J.T. Koerber, D.W. Pack. "Polyethylenimine Derivatives with Reduced Buffering Capacity and Enhanced Transfection Efficiency." *Pharm. Res.* 21: 365-371 (2004). PMID: 15032320
4. Forrest, M.L., N. Gabrielson, D.W. Pack. "Cyclodextrin-polyethylenimine conjugates for targeted in vitro gene delivery." *Biotechnol. Bioeng.* 89: 416-423 (2005). PMID: 15627256
5. Kwon, G.S. and M.L. Forrest. "Amphiphilic Block Copolymer Micelles for Nanoscale Drug Delivery." *Drug Dev. Res.* 67: 15-22 (2006).
6. Forrest, M.L., C.-Y. Won, A.W. Waseem, G.S. Kwon. "In vitro Release of the mTOR Inhibitor Rapamycin from Poly(ethylene glycol)-b-Poly(ϵ -caprolactone) Micelles." *J. Control. Release* 110:370-377 (2006). PMID: 16298448
Highest cited paper in this journal for 2006.
7. Forrest, M.L., A. Zhao, C.-Y. Won, A.W. Waseem, G.S. Kwon. "Lipophilic prodrugs of Hsp90 inhibitor geldanamycin for nanoencapsulation in poly(ethylene glycol)-beta-poly(sigma-caprolactone) micelles." *J. Control. Release* 116:139-149 (2006). PMID: 16926059
8. Xiong, M.P., M.L. Forrest, A.L. Karls, G.S. Kwon. "Biotin-triggered release of PEG-avidin from biotinylated-PEI enhances in vitro gene expression." *Bioconjug. Chem.* 18:746-753 (2007). PMID: 17375897
9. Yáñez, J.A., M.L. Forrest, Y. Ohgami, G.S. Kwon, N.M. Davies. "Pharmacometrics and Delivery of Novel Nanoformulated PEG-b-Poly(ϵ -caprolactone) Micelles of Rapamycin." *Cancer Chemo. Pharmacol.* 2007 61(1):133-144 (2008). PMID: 17393166 PMCID: PMC2259393
10. Xiong, M.P., Y. Bae, S. Fukushima, M.L. Forrest, N. Nishiyama, K. Kataoka, G.S. Kwon. "pH-Responsive Multi-PEGylated Dual Cationic Nanoparticles Enable Charge Modulations for Safe Gene Delivery." *ChemMedChem* 2(9): 1321-1327 (2007). PMID: 17579918
11. Xiong, M.P., M.L. Forrest, N.M. Davies, G.S. Kwon. "Poly(Aspartate-g-PEI800), a polyethylenimine analogue of low toxicity and high transfection efficiency for gene delivery." *Biomaterials* 28:4889-4900 (2007). PMID: 17692910.
12. Forrest, M.L., J.A. Yáñez, C.M. Remsberg, Y. Ohgami, G.S. Kwon, N.M. Davies. "Paclitaxel prodrugs with sustained release and high solubility in poly(ethylene glycol)-b-poly(ϵ -caprolactone) micelle nanocarriers: pharmacokinetic disposition, tolerability and cytotoxicity." *Pharm. Res.* 25:194-206 (2008). PMID:17912488.

13. M.L. Forrest, G.S. Kwon. "Clinical developments in drug delivery nanotechnology." *Adv. Drug Deliv. Rev.* 60(8): 861-862 (2008). PMID: 18358557.
14. S. Cai, Y. Xie, T. Bagby, M.S. Cohen, M.L. Forrest. "Intralymphatic chemotherapy using a hyaluronan-cisplatin conjugate." *J. Surg. Res.* 147(2): 247-252 (2008). PMID: 18498877. **Featured on issue cover.** PMCID: PMC2430723.
15. M.P. Xiong, J.A. Yáñez, C.M. Remsberg, Y. Ohgami, G.S. Kwon, N.M. Davies, M.L. Forrest. "Formulation of a geldanamycin prodrug in mPEG-b-PCL micelles greatly enhances tolerability and pharmacokinetics in rats." *J. Control. Rel.* 129(1):33-40 (2008). PMID: 18456363 PMCID: PMC2492396
16. K.R. Vega-Villa, J.A. Yáñez, C.M. Remsberg, M.L. Forrest, N.M. Davies. "Clinical Toxicities of Nanocarrier Systems." *Adv. Drug Deliv. Rev.* 60(8):929-938 (2008). PMID: 18313790
17. K.L. Aillon, Y. Xie, N. El-Gendy, C.J. Berkland, M.L. Forrest. "Effects of nanomaterial physicochemical properties on in vivo toxicity." *Adv. Drug. Deliv. Rev.*, 61(6):457-66 (2009). PMID 19386275. PMCID: PMC2743376
18. M.P. Xiong, J.A. Yáñez, G.S. Kwon, N.M. Davies, M.L. Forrest. "A cremophor-free formulation for tanespirmycin (17-AAG) using PEO-b-PDLLA micelles: characterization and pharmacokinetics in rats." *J. Pharm. Sci.* 98(4):1577-86 (2009). PMID 18752263 PMCID: PMC2649998
19. Xie, Y, M.S. Cohen, M.L. Forrest. "Drug Delivery to the Lymphatic System: Importance in Future Cancer Diagnosis and Therapies." *Expert Opin. Drug Deliv.*, 6:785-92 (2009). PMID: 19563270. PMCID: PMC3102644.
20. S.K. Nune, P. Gunda, P.K. Thallapally, Y.Y. Lin, M.L. Forrest, C.J. Berkland. "Nanoparticles for biomedical imaging." *Expert Opin. Drug Deliv.* 6(11):1175-94 (2009). PMID: 19743894. PMCID: PMC3097035.
21. M.S. Cohen, S. Cai, M.L. Forrest. "A Novel Intralymphatic Nanocarrier-Delivery System for Cisplatin Therapy in Breast Cancer with Improved Tumor Efficacy and Lower Systemic Toxicity In Vivo." *Am. J. Surg.*, 198(6):781-6 (2009). PMID 19969129. PMCID: PMC2791715.
22. S. Cai, Y. Xie, N.M. Davies, M.S. Cohen, M.L. Forrest. "Pharmacokinetics and disposition of a localized lymphatic polymeric hyaluronan conjugate of cisplatin in rats." *J. Pharm. Sci.*, 99(6):2664-71 (2010). PMID: 19960530
23. R. Ndolo, M.L. Forrest, J.P. Krise. "The role of lysosomes in limiting drug toxicity in mice." *J. Pharmacol. Exp. Ther.* 333(1):120-8 (2010). PMID: 20056778 PMCID: PMC2846018
24. D.A. Rao, M.L. Forrest, A.W. Alani, G.S. Kwon, J.R. Robinson. "Biodegradable PLGA based nanoparticles for sustained regional lymphatic drug delivery." *J. Pharm. Sci.*, 99(4):2018-31 (2010). PMID: 19902520
25. Y. Xie, K.L. Aillon, S. Cai, J.M. Christian, N.M. Davies, C.J. Berkland, M.L. Forrest. "Pulmonary delivery of cisplatin-hyaluronan conjugates via endotracheal instillation for the treatment of lung cancer." *Intl. J. Pharm.* 392(1-2):156-63 (2010). PMID: 20363303 PMCID: PMC2873163
26. S. Cai, S. Thati, T.R. Bagby, H-M. Diab, N.M. Davies, M.S. Cohen, M.L. Forrest. "Localized doxorubicin chemotherapy with a biopolymeric nanocarrier improves survival and reduces toxicity in xenografts of human breast cancer." *J. Control. Rel.* 146(2):212-218 (2010). PMID: 20403395 PMCID: PMC2918704
27. Y. Xie, S. Duan, M.L. Forrest. "Alkyne- and 1,6-elimination- succinimidyl carbonate- terminated heterobifunctional poly(ethylene glycol) for reversible "click" PEGylation." *Drug Discov. Ther.* 4(4):240-245 (2010). PMID: 21949558 PMCID: PMC3178183
28. S. Cai, N.M. Davies, M.S. Cohen, M.L. Forrest. "Carried-based intralymphatic cisplatin chemotherapy for the treatment of metastatic squamous cell carcinoma of the head & neck." *Ther. Deliv.* 1(2):237-245 (2010). PMID: 21339844 PMCID: PMC3039877
29. R. A. Ndolo, D.T. Jacobs, M.L. Forrest, J.P. Krise. "Intracellular distribution-based anticancer drug targeting: exploiting a lysosomal acidification defect associated with cancer cells." *Mol. Cell Pharmacol.* 2(4):131-126 (2010). PMID: 21274418 PMCID: PMC3026327
30. J.A. Yáñez, C.M. Remsberg, C.L. Sayre, M.L. Forrest, N.M. Davies. "Flip-flop pharmacokinetics – reversal of disposition. Challenges and opportunities during drug development." *Ther. Deliv.* 2(5):643-672 (2011). PMID: 21837267 PMCID: PMC3152312
31. S.K. Nune, P. Gunda, B.K. Majeti, P.K. Thallapally, M.L. Forrest. "Advances in lymphatic imaging and drug delivery." *Adv. Drug. Deliv. Rev.* 63(10-11):867-85 (2011). PMID: 21718728. PMCID: 3164439.
32. S. Cai, Q. Yang, M.L. Forrest. "Lymphatic drug delivery using engineered liposomes and solid lipid nanoparticles." *Adv. Drug. Deliv. Rev.* 63(10-11):901-908 (2011). PMID: 21712055. PMCID: PMC3164476.
33. M.S. Cohen, M.L. Forrest. "Lymphatic drug delivery: Therapy, Imaging and Nanotechnology." *Adv. Drug. Deliv. Rev.* 63(10-11):865-866 (2011). PMID: 21669240
34. S.M. Cohen, R. Mukerji, S. Cai, I. Damjanov, M.L. Forrest*, M.S. Cohen*. "Subcutaneous delivery of nanoconjugated doxorubicin and cisplatin for locally advanced breast cancer demonstrate improved efficacy and decreased toxicity at lower doses than standard systemic combination therapy in vivo." *Am. J. Surg.* 202(6):646-653 (2011) * co-corresponding authors PMID: 21982998.
35. V. Shum, N. Gabrielson, M.L. Forrest, D.W. Pack. "The effects of PVP(Fe(III)) Catalyst on polymer molecular weight and gene delivery via biodegradable cross-linked polyethylenimine." *Pharm. Res.* 29(2):500-10 (2011). PMID: 21892707 PMCID: PMC3465843
36. S. Cai, T. Bagby, M.L. Forrest. "Development of regional chemotherapies: feasibility, safety and efficacy in clinical use and preclinical studies." *Ther. Deliv.* 2(11):1467-1484 (2011). PMID: 22229080 PMCID: PMC3249754

37. Q. Yang, H. Cui, S. Cai, X. Yang, M.L. Forrest. "In vivo photoacoustic imaging of chemotherapy-induced apoptosis in squamous cell carcinoma using a near-infrared caspase-9 probe" *J. Biomed. Optics*. 16(11):116026 (2011) PMID: 22112131 PMCID: PMC3221716
Included in: Virtual Journal of Biological Physics, 22(9) (2011).
38. Y. Luan, Q. Yang, Y. Xie, S. Duan, S. Cai, M.L. Forrest. "A Sensitive Near-Infrared Fluorescent Probe for Caspase: Synthesis and Application in Cell Imaging." *Drug Discov. Ther.* 5(5):220-226 (2011). PMID: 22282719 PMCID: PMC3265084
39. S. Sharifi, S. Behzadi, S. Laurent, M.L. Forrest, P. Stroeve, M. Mahmoudi. "Toxicity of Nanomaterials." *Chem. Soc. Rev.* 41: 2323-2343 (2012). PMID: 22170510 **Featured as most read article in Dec11 and Jan12.**
40. S. Duan, S. Cai, Q. Yang, M. L. Forrest. "Multi-arm polymeric nanocarrier as a nitric oxide delivery platform for chemotherapy of head and neck squamous cell carcinoma" *Biomaterials* 33(11):3243-3253 (2012). PMID: 22281420 PMCID: PMC3572206
41. S. Duan, S. Cai, Y. Xie, T.R. Bagby, M.L. Forrest. "Synthesis and characterization of a multi-arm poly(acrylic acid) star polymer for application in delivery of cisplatin and a nitric oxide." *J. Polym. Sci. A Polym. Chem.* 50(13): 2715-24 (2012).
42. Y. Zhao, S. Duan, X. Zeng, C. Liu, B. Li, M.L. Forrest. "Prodrug strategy for PSMA-targeted delivery of TGX-221 to prostate cancer cells" *Mol. Pharm.* 9(6):1705-16 (2012). PMID: 22494444 PMCID: PMC3601665
43. T. R. Bagby, S. Cai, S. Thati, S. Duan, D.J. Aires, M.L. Forrest. "Impact of Molecular Weight on Lymphatic Drainage of a Biopolymer-Based Imaging Agent." *Pharmaceutics* 4, 276-295 (2012). PMID: 24300232 PMCID: PMC3834911
44. E.A. Mohamed, M. M. Meshali, C.M. Remsberg, Yunqi Zhao, T.M. Borg, A. Monem, M. Foda, N.M. Davies, M.L. Forrest. "Vorinostat with Sustained Release and High Solubility in Poly(ethylene glycol)-b-poly(DL-lactic acid) Micelle Nanocarriers: Characterization and Effects on Pharmacokinetics in Rat Serum and Urine" *J. Pharm. Sci.* 101(10):3787-98 (2012). PMID: 22806441
45. R. Ndolo, Y. Luan, S. Duan, M.L. Forrest, J. Krise. "Lysosomotropic Properties of Weakly Basic Anticancer Agents Promote Cancer Cell Selectivity" *PLoS One* 7(11):e49366 (2012). PMID 23145164 PMCID: PMC3492287
46. C. Remsberg, Y. Zhao, J. Takemoto, R. Bertram, N. Davies, M.L. Forrest. "Pharmacokinetic Evaluation of a DSPE-PEG2000 Micellar Formulation of Ridaforolimus in Rat." *Pharmaceutics* 5(1):81-91 (2012)
47. R. Venable, D. Worley, D. Gustafson, R. Hansen, E.J. Ehrhart, D. Aires, S. Cai, M. Cohen, M.L. Forrest. "Hyaluronan cisplatin conjugate in five dogs with soft tissue sarcomas." *Am. J. Vet. Res.* 73(12):1969-76 (2012). PMID: 23176425 PMCID: PMC3778682
48. T.R. Bagby, S. Duan, S. Cai, S. Thati, C. Berkland, D. Aires, M.L. Forrest. "Lymphatic trafficking kinetics and near-infrared imaging using star polymer architectures with controlled anionic character". *Eur. J. Pharm. Sci.* 47(1):287-94 (2013). PMID 22546180 PMCID: PMC4301975
49. A.J. Mellot, M.L. Forrest, M.S. Detamore. "Physical non-viral gene delivery methods for tissue engineering." *Ann. Biomed. Eng.* 41(3):446-68 (2013) PMID: 23099792
50. K. Devarajan, M.L. Forrest, M.S. Detamore, H. Staecker. "Adenovector Mediated Delivery to Human Umbilical Cord Mesenchymal Stromal Cells Induces Inner Ear Cell Phenotype." *Cellular Reprogramming* 15(1):43-54 (2013). PMID: 23379581 PMCID: PMC4298749
51. S. Cohen, N. Rockefeller, R. Makerji, D. Durham, M. Forrest, S. Cai, M. Cohen, Y. Shnayder. "Efficacy and Toxicity of Peritumoral Delivery of Nanoconjugated Cisplatin in an In Vivo Murine Model of Head and Neck Squamous Cell Carcinoma." *JAMA Otolaryngology-Head & Neck Surgery* 139(4):382-7 (2013). PMID: 23599074 PMCID: PMC4306558
52. T. Zhang, H. Cui, H-C. Chang, X. Yang, M.L. Forrest. "Photoacoustic imaging of biological tissues with radiation damaged nanodiamonds as a near infrared optical contrast agent." *Journal of Biomedical Optics*. 18(2):26018 (2013). PMID: 23400417 PMCID: PMC3569583
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54. Q. Yang, D.J. Aires, S. Cai, G.R. Fraga, D. Zhang, C.Z. Li, M.L. Forrest. "In vivo efficacy of nano hyaluronan-conjugated cisplatin for treatment of murine melanoma." *J. Drugs Dermatol.* 13(3):283-7 (2014). PMID: 24595572 PMCID: PMC4344317
55. Mellott AJ, Godsey ME, Shinogle HE, Moore DS, Forrest ML, Detamore MS, "Improving viability and transfection efficiency with human umbilical cord Wharton's jelly cells through use of a ROCK inhibitor," *Cellular Reprogramming* 16(2):91-7 (2014). PMID: 24552552 PMCID: PMC3967373
56. C. Louizos, J.A. Yanez, M.L. Forrest, N.M. Davies. "Deconvoluting the Hysteresis Loop Conundrum in Pharmacokinetic / Pharmacodynamic Relationships" *J. Pharm. Pharm. Sci.* 17(1):34-91 (2014). PMID: 24735761 PMCID: PMC4332569
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59. S. Cai, A. Alhowyan, Q. Yang, W.C.M. Forrest, Y. Shnayder, M.L. Forrest. "Cellular Uptake and Internalization of Hyaluronan-based Doxorubicin and Cisplatin Conjugates." *J. Drug Targeting*, 22(7):648-57 (2014). PMID: 24892741
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62. Q. Yang, K.R. Moulder, M.S. Cohen, S. Cai, M.L. Forrest. "Cabozantinib Loaded DSPE-PEG2000 Micelles as Delivery System: Formulation, Characterization and Cytotoxicity Evaluation." *BAOJ Pharm. Sci.* 1.pii:001 (2015). PMID: 25688382 PMCID: PMC4327881
63. T. Zhang, Q. Yang, W.C. Forrest, S. Cai, D. Aires, M.L. Forrest. "A Lanthanum-Tagged Chemotherapeutic Agent HA-Pt to Track the *In Vivo* Distribution of Hyaluronic Acid Complexes." *BAOJ Pharm. Sci.* 1.pii:002 (2015). PMID: 26756040 PMCID: PMC4706177.
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58. K. Devarajan, M.L. Forrest, H. Staecker, M.S. Detamore. "Adenoviral mediated gene delivery to human umbilical cord mesenchymal stem cells for inner ear hair cell differentiation." Biomedical Engineering Society, Hartford, CT, October, 2011.
59. C.L. Sayre, S.E. Martinez, E.A. Mohamed, M.M. Meshali, C.M. Remsberg, Y. Zhao, T. M. Borg. A.M.M. Foda, J.K. Takemoto, M.L. Forrest, N.M. Davies. "Vorinostat with sustained released and high solubility in poly(ethylene glycol)-b-poly(DL-lactic acid) micelle nanocarriers: characterization and effects on pharmacokinetics in rat serum and urine." Canadian Society for Pharmaceutical Sciences Annual Symposium, Toronto, June 2012.
60. S. Cai, Q. Yang, S. Siller, D. Worley, L. Schneider, D. Aires, M. Cohen, M.L. Forrest. "A safe and efficacious approach to cisplatin chemotherapy: loco-regional injection of HylaPlat in canines." American Association of Pharmaceutical Scientists Annual Meeting, Chicago, IL, October, 2012.
61. Forrest, M.L. "Formulation development and pharmacokinetics of subcutaneously injected HylaPlat in spontaneous canine cancers" International Society for Hyaluran Sciences. Oklahoma City, OK. June 3, 2013.
62. T. Zhang, Forrest, M.L. "Nanodiamond-based contrast agents for photoacoustic imaging." SPIE International Society for optics and photonics. San Diego, CA. August 25, 2013.
63. S. Cai, D. Vartia, M. Forrest, J. Bryan, D. Aires, M.L. Forrest. "A safe and efficacious approach to cisplatin chemotherapy: loco-regional injection of HylaPlat in canines." American Association of Cancer Research Annual Meeting, San Diego, CA, April 2014.
64. S. Cai, W.C. Forrest, J. Bryan, D. Aires, M.L. Forrest. "Development of Locoregional Polymeric Cisplatin Chemotherapy: Clinical Trials in Canines with Spontaneous Cancers" Controlled Release Society Annual Meeting, Chicago, IL, June 2014.
65. M. L. Forrest, S. Cai, W.C. Forrest, T. Zhang, M. Cohen, J. Bryan, D. Aires. "Development of Locoregional Polymeric Cisplatin Chemotherapy: Clinical Trials in Canines with Spontaneous Cancers," American Association for Pharmaceutical Sciences (AAPS) Annual Conference, San Diego, CA, November 2014
66. P.T. White, C. Subramanian, P.T. Grogan, S. Cai, M.L. Forrest, M.S. Cohen. "Nanoparticle-targeting of breast cancer stem cells improves efficacy and durability of chemotherapy." Association for Academic Surgery Congress, Las Vegas, NV, February 2015.
67. S. Ishiguro, D. Uppalapati, S. Cai, J. Hodge, L. Forrest, M. Tamura. "A local chemotherapy with hyaluronan-cisplatin conjugate significantly attenuates growth of lung adenocarcinoma xenografts in mouse model," American Association for Cancer Research (AACR) Annual Conference, Philadelphia, PA, April 22, 2015.
68. Samaa Alrushaid, Casey L. Sayre, Zaid Al Maayh, Yunqi Zhao, M Laird Forrest, Sanjeewa Senadheera, Kevin Chaboyer, Hope D Anderson, Ayman El-Kadi and Neal M. Davies "Mechanistically Elucidating the *In-Vitro* Safety and Efficacy of a Novel Doxorubicin Derivative." American Association for Pharmaceutical Sciences (AAPS) Annual Conference, Denver, CO, November 2016.
69. Peter Kleindl, S. P. Sanjeewa Nilendra Senadheera, Samantha Farb, M. Laird Forrest. "Development of novel immunosuppressant prodrugs for treatment of ulcerative colitis." Federation of American Societies for Experimental Biology (FASEB) Gastrointestinal Tract XVII: Current Biology of the GI Tract, Mucosa, Microbiota, and Beyond. Steamboat Springs, CO. July 30-Aug 4, 2017.

70. Ninad Varkhede, Christian Schoeneich, Laird Forrest. "Pre-systemic In Vitro Metabolism of Therapeutic Proteins After Subcutaneous Administration and Its Utility for a Semi-PBPK Model" American Association for Pharmaceutical Sciences (AAPS) Annual Conference, San Diego, CA, November 2017
71. K. R. Moulder, F. J. Martinez-Becerra, W. L. Picking, M. L. Forrest. "Enhancing immunological response towards Shigella spp. through a multivalent subunit vaccine" American Association for Pharmaceutical Sciences (AAPS) Annual Conference, San Diego, CA, November 2017
72. R. Lu, C. Groer, K.R. Moulder, P.A. Kleindl, M.L. Forrest. "An extended release formulation of toll like receptor 7 agonist analogs." KU Pharm Chem. Fall Retreat. Oct. 2018
73. Peter A. Kleindl, S. P. Sanjeeva Nilendra Senadheera, M. Laird Forrest. (October 2018) "Targeted delivery of potent immunosuppressants for treatment of ulcerative colitis." Department of Pharmaceutical Chemistry Annual Fall Retreat, Lawrence, Kansas.
74. Peter A. Kleindl, S. P. Sanjeeva Nilendra Senadheera, M. Laird Forrest. (September 2018) "Targeted delivery of potent immunosuppressants for treatment of ulcerative colitis." Globalization of Pharmaceutics Education Network (GPEN) 2018 Conference, Singapore.
75. Peter A. Kleindl, Jian Xiong, Asha Hewarathna, Maulik K. Nariya, Olivier Mozziconacci, Jae Hyun Kim, Sangeeta B. Joshi, C. Russell Middaugh, Christian Schöneich, Eric J. Deeds, David B. Volkin, M. Laird Forrest. (January 2018) "Physicochemical and biological characterization of crofelemer for identification of critical quality attributes using a machine learning approach," 33rd Graduate Honors Symposium, Lawrence, Kansas.
76. Moulder KR, Zhang T, Forrest ML, "Development and biophysical characterization of a sustained release formulation for Coversin, a C5 Complement Inhibitor." *Department of Pharmaceutical Chemistry Annual Fall Retreat, 2018*
77. Hunt, J; Kleindl, P; Forrest, L. "Further exploration of the SAR of imidazoquinolines; Identification of potent C7 substituted imidazoquinolines" *Department of Pharmaceutical Chemistry Annual Fall Retreat, 2018*
78. Brachtenbach A, Moulder KR, Forrest ML, "Development and characterization of a novel nanoparticle for the sustained release of antigens following subcutaneous injection." *Undergraduate Research Symposium, University of Kansas, 2018*
79. Brachtenbach A, Moulder KR, Forrest ML, "Development of nanodiamonds as a vaccine delivery system." *Summer Undergraduate Research Poster Session, University of Kansas, 2018*

Invited Lectures and Conference Podium Presentations (chronological order)

1. M.L. Forrest, D.W. Pack. "Quantitative assay for polyplex release from endolysosomes: implications for design of gene delivery vehicles." AIChE Annual Meeting, Los Angeles, CA, November 13, 2000.
2. M.L. Forrest, D.W. Pack. "Quantitation of endolysosomal trafficking of polyplex gene delivery vehicles." 28th International Symposium on Controlled Release of Bioactive Materials, San Diego, California, June 27, 2001.
3. Forrest, M.L. and D.W. Pack. "Intelligent Design of Gene Delivery Vehicles: Is Endosomal Buffering Necessary?" American Institute of Chemical Engineering National Meeting, Reno, NV, November 2001.
4. Forrest, M.L. and D.W. Pack. "A Degradable Derivative of Polyethylenimine that Provides Higher Gene Transfer Efficiency and Negligible Cytotoxicity." American Institute of Chemical Engineering Annual National Meeting, Indianapolis, IN, November 2002.
5. M.L. Forrest, J.T. Koerber, D.W. Pack. "Non-viral gene delivery vectors based on modified polyethylenimine." 30th International Symposium on Controlled Release of Bioactive Materials, Glasgow, Scotland, June 22, 2003.
6. M.L. Forrest, J.T. Koerber, D.W. Pack. "Highly efficient, biodegradable polyethylenimine gene delivery vehicles." 30th International Symposium on Controlled Release of Bioactive Materials, Glasgow, Scotland, June 22, 2003.
7. M.L. Forrest, J.T. Koerber, and D.W. Pack. "Enhancement of PEI-mediated gene delivery by acetylation of primary and secondary amines." AIChE Annual Meeting, San Francisco, CA, November 20, 2003.
8. N. Gabrielson, M.L. Forrest, and D.W. Pack. "Reduction of polyethylenimine buffering capacity enhances in-vitro gene delivery activity." American Society of Gene Therapy 7th Annual Meeting, Minneapolis, MN, June 4, 2004.
9. Forrest, M.L. and G.S. Kwon. "Phospholipid Micelles for Chemotherapeutic Drug Delivery." Invited lecture for Engineering Seminar Series, University of Kansas, Lawrence, KS, March 10, 2005.
10. Forrest, M.L. and G.S. Kwon. "Nanoencapsulation of Chemotherapeutics." Invited lecture for Pharmaceutical Sciences Seminar Series, Washington State University, Pullman, WA, September 9, 2005.

11. Forrest, M.L. and G.S. Kwon. "Development of Nanotechnologies for Drug and Gene Delivery." Invited lecture for Chemical Engineering, Florida State University, April 25, 2006.
12. Forrest, M.L. "Stability of Sirolimus in oxidative environments." Invited lecture for Exogenesis Inc., Cambridge, MA, April 25, 2007.
13. Forrest, M.L. "Emerging nanotherapeutics for cancer." Invited lecture for Sigma Xi Seminar Series, School of Medicine, University of Kansas Medical Center, Kansas City, KS, September 3, 2007.
14. Forrest, M.L. "Nanocarrier technologies for cancer imaging and treatment." Invited lecture for Engineering Seminar Series, University of Kansas, Lawrence, KS, October 19, 2007.
15. Forrest, M.L. "Nanocarrier technology in the treatment and diagnosis of cancer." Invited lecture for Department of Chemistry, Missouri State University, Springfield, MO, October 29, 2007.
16. Forrest, M.L. "New routes for chemotherapeutic intervention using nanotechnology." Invited lecture for Department of Molecular and integrative physiology, University of Kansas Medical Center, Kansas City, MO, February 4, 2008.
17. Forrest, M.L. "Trailblazing new pathways in cancer therapy", Invited lecture for Department of Chemical Engineering, Oklahoma State University, Stillwater, OK, October 7, 2008.
18. Forrest, M.L. "Lymphatic chemotherapy for localized cancers", Invited lecture for Department of Oral Biology, University of Missouri, Kansas City, KS, December 6, 2008.
19. Forrest, M.L. "Drug delivery technology and new treatments in cancer." Invited lecture for Department of Chemistry, University of Central Arkansas, Conway, AR, November 20, 2008.
20. Forrest, M.L. "Design of nanocarriers for novel routes of therapy." Invited lecture for Department of Bioengineering, University of Kansas, KS, April 10, 2009.
21. Forrest, M.L. "Drug nanocarriers for intralymphatic chemotherapy of breast cancer." INBRE Conference, Oklahoma City, OK, May 28, 2009.
22. Forrest, M.L. "Targeted Nanopharmaceuticals for Localized Carcinomas", Tsukuba University, Tsukuba City, Japan, July 15, 2009.
23. Forrest, M.L. "Nanotechnology Treatments for Cancer", Shandong University, Jinan, China, July 27, 2009.
24. Forrest, M.L. "Nanotechnology and Future Therapeutics in Cancer Treatment", Washington State University, Pullman, WA, August 3, 2009.
25. Forrest, M.L., "Development of Nanocarrier Platforms for Locally Advanced Carcinomas", Washington State University, Pullman, WA, August 7, 2009.
26. Forrest, M.L. "Localizing drug delivery to reduce toxicity and improve efficacy." NSF IUCRC, Atlanta, GA, November 20, 2009.
27. Forrest, M.L. "Nanoconjugate Formulation for Localized Chemotherapy." Invited speaker for NanoDDS, Indianapolis, IN, October 6, 2009.
28. Forrest, M.L. "Star Polymers for Lymphatic Delivery." Invited speaker for American Chemical Society Midwest Regional Annual Meeting, Iowa City, IA, October 23, 2009.
29. Forrest, M.L. "Engineered nanomaterials in drug delivery." Department of Materials Science Technology, Graduate School of Industrial Science and Technology, Tokyo University of Science, Tokyo, Japan, June 9, 2010.
30. Forrest, M.L. "Nanoconjugate formulation for treatment of locally advanced cancers." Department of Biomolecular Engineering, Graduate School of Bioscience and Biotechnology, Tokyo Institute of Technology, Tokyo, Japan, June 11, 2010.
31. Forrest, M.L. "Nanoconjugate formulation for treatment of locally advanced cancers." Bioengineering Laboratory, RIKEN Institute, Wako, Japan, June 15, 2010.
32. Forrest, M.L. "Engineered nanomaterials in drug delivery." Bioengineering Department, Tokyo University of Agriculture, Tokyo, Japan, June 22, 2010.
33. Forrest, M.L. "Star polymers for localized drug delivery." Graduate School of Medicine, University of Tokyo, Tokyo, Japan, June 23, 2010.
34. Forrest, M.L. "Lymphatic drug targeting systems." Biomaterials Engineering Research Institute, Tokyo Medical and Dental, Tokyo, Japan, June 28, 2010.
35. Forrest, M.L. "Localized chemotherapy using polymeric nanocarriers." Department of Translational Medicine, National Cancer Center, Tokyo, Japan, July 1, 2010.
36. Forrest, M.L. "Nanoparticle engineering for targeted drug delivery." School of Engineering, Tsukuba University, Tsukuba City, Japan, July 6, 2010.

37. Forrest, M.L. "Hyaluronan nanocarriers in drug delivery." Department of Biophysical Chemistry, Kyoto Pharmaceutical University, Kyoto, Japan, July 8, 2010.
38. Forrest, M.L. "Star polymers for localized drug delivery." Department of Drug Delivery Research and Institute for Innovative NanoBio Drug Delivery and Development, Graduate School of Pharmaceutical Sciences, Kyoto University, Kyoto, Japan, July 9, 2010.
39. Forrest, M.L. "Localized chemotherapy using polymeric nanocarriers." Department of Applied Chemistry, Graduate School of Engineering, Osaka University, Osaka, Japan, July 12, 2010.
40. Forrest, M.L. "Nanoparticle strategies for treatment of head and neck and breast cancers." Department of Biomedical Engineering, National Cerebral and Cardiovascular Center Research Institute, Osaka, Japan, July 13, 2010.
41. Forrest, M.L. "Star polymers for localized drug delivery." Department of Chemistry and Materials Engineering, Faculty of Chemistry, Materials and Bioengineering, Kansai University, Osaka, Japan, July 14, 2010.
42. Forrest, M.L. "Localized chemotherapy using polymeric nanocarriers." Osaka Prefecture University, Osaka, Japan, July 15, 2010.
43. Forrest, M.L. "Localized chemotherapy using polymeric nanocarriers." Department of Applied Chemistry and Bioengineering, Graduate School of Engineering, Osaka City University, Osaka, Japan, July 16, 2010.
44. Forrest, M.L. "Multi-branched polymer design for drug delivery." Department of Applied Chemistry, Hiroshima University, Hiroshima, Japan, July 17, 2010.
45. Forrest, M.L. "Localized nanoparticle chemotherapy." Institute for Materials Chemistry and Engineering." Kyushu University, Fukuoka, Japan, July 20, 2010.
46. Forrest, M.L. "Targeted chemotherapy in the lymphatic system." Hokkaido University, Sapporo, Japan, July 27, 2010.
47. S. Cai, M.L. Forrest. "Development of Drug Delivery Platforms for Locoregional Treatment of Carcinomas." Presented at Kansas IDeA Network of Biomedical Research Excellence Symposium, Kansas City, Kansas, January 15, 2011
48. Forrest, M.L. "Targeted drug delivery to the lymphatics and functional imaging of tumor response." Affiliated Hospital of Guangdong Medical College, Zhanjiang, China, June 3, 2011.
49. Forrest, M.L. "Targeted chemotherapy platform for veterinarian oncology." University of Missouri, Rolla, October 7, 2011.
50. Forrest, M.L. "Localized chemotherapy for anti-cancer treatment and rapid in vivo imaging of therapeutic response." University of Kentucky, Dept. Pharmaceutics Sciences, Lexington, KY, November 4, 2011.
51. Forrest, M.L. "Development of localized cancer treatments and measurement of therapeutic response." University of Manitoba, School of Pharmacy, Winnipeg, Canada, April 11, 2012.
52. Forrest, M.L. "Localized anti-cancer treatment via lymphatic targeting." Midwest Regional Meeting of the American Chemical Society (MWMB), Omaha, Nebraska, October 25, 2012.
53. Forrest, M.L. "Localized anti-cancer treatment via lymphatic targeting." KINBRE External Advisory Committee, Kansas City, KS, April 17, 2013.
54. Forrest, M.L. "Localized anti-cancer chemotherapy." International Advanced Drug Delivery Symposium. Taipei, Taiwan, May 2, 2013.
55. Forrest, M.L. "Formulation development and pharmacokinetics of subcutaneously injected HylaPlat in spontaneous canine cancers" International Society for Hyaluran Sciences. Oklahoma City, OK. June 3, 2013.
56. Forrest, M.L., T. Zhang. "Nanodiamond-based contrast agents for photoacoustic imaging." Invited speaker for International Society for Optics and Photonics (SPIE), San Diego, CA, August 27, 2013.
57. Forrest, M.L. "Locally targeted anti-cancer therapy." University of Missouri – Kansas City. Kansas City, MO. April 27, 2014.
58. Forrest, M.L. "Locally targeted platinum chemotherapy." Kansas State University, Manhattan, KS. October 5, 2015.
59. Forrest, M.L. "Particle-based Lymphatic targeted chemotherapy." University of Alberta, Edmonton, Alberta, Canada. October 12, 2016.
60. Forrest, M.L. "Particle Therapy in the Treatment of Lymphatic Cancers" Globalization of Pharmaceutics Education Network (GPEN) Conference, Lawrence, KS. November 12, 2016.
61. Forrest, M.L. "Particle based lymphatic cancer treatment: Preclinical and canine clinical studies" University of Kansas Cancer Center seminar series, Kansas City, KS. December 2, 2016.
62. Peter A. Kleindl, Jian Xiong, Asha N. Hewarathna, Maulik K. Nariya, Olivier Mozziconacci, Jae Hyun Kim, Sangeeta B. Joshi, C. Russell Middaugh, Christian Schöneich, Eric J. Deeds, David B. Volkin, M. Laird Forrest. *Characterization of the oligomeric proanthocyanidin crofelemer toward development of an integrated mathematical model for comparison of complex therapeutics*. Presented at 32nd Graduate Honors Symposium, Lawrence, KS. (January 11, 2017)

63. Forrest, M.L. "Targeting the lymphatics to improve cancer treatment." Tokyo, Japan. May 10, 2017.
64. Ninad Varkhede, C. Russell Middaugh, Christian Schöneich, M. Laird Forrest. *Effect of iron oxide nanoparticles on secondary structure and oxidation of rat growth hormone*. Presented at 33rd Graduate Honors Symposium, Lawrence, KS (January 17, 2018)
65. Forrest, M.L. "Development of localized drug delivery systems." University of Missouri, Columbia, MO, August 28, 2018.
66. Forrest, M.L. "Development and pre-clinical testing of localized drug delivery systems in canines with spontaneous cancers." Invited speaker, NanoDDS Annual Conference, Portland, OR, Sept. 23, 2018.
67. Forrest, M.L. "Development of localized therapies for cancer." University of Wisconsin, Madison, WI, October 12, 2018.
68. Forrest, M.L. "Development of localized immunochemotherapy in canines with spontaneous cancers", Controlled Release Society Annual Conference (Canadian Chapter) invited speaker, Vancouver, BC, May 22, 2019.

Thesis Committees, Past Students

Thesis committee chair:

PhD: Taryn Bagby (Pharm Chem, 2012), Shuang Cai (Pharm Chem, 2011), Jordan Hunt (Medicinal Chemistry, expected 2019), Peter Kleide (Pharm Chem, expected 2020), Ryan Moulder (Pharm Chem, 2019), Ninad Varkhede (Pharm Chem, 2018), Qiuhong Yang (Pharm Chem, 2014), Ti Zhang (Pharm Chem, 2015), Yunqi Zhao (Pharm Chem, 2013)

MS: Adel Alhowyan (Pharm Chem, 2014), David Hart (Pharm Chem, 2007), Jordan Hunt (Med. Chem, 2018), Peter Kleindl (Bioengineering, 2016), Ryan Moulder (Bioengineering, 2016), Abby Petrulis (Pharm Chem, 2018), Alisha Simonian (Pharm Chem, expected 2019), Evelyn Yanez (Pharm Chem, 2018)

Thesis committee member:

PhD: Rosemary Ndolo (Pharm Chem, 2012), Julian Kissman (Pharm Chem, 2009), Chuda Chittasupho (Pharm Chem, 2012), Ryan Funk (Pharm Chem), Supang Kondee (Pharm Chem, 2011), Kwame Nti-Addae (Pharm Chem, 2008), Zahra Mohammadi (Chem Engr), Erik Vankampen (Chem Engr), Tiffany Suekama (Bioengineering, 2014), Jacob Staley (Bioengineering), Amir Fakhari (Bioengineering, 2011), Huizhong Cui (Bioengineering, 2012), Janggun Jo (Bioengineering, 2014), Lindsey Ott (Bioengineering, 2014), Anahita Khanlari (Chem Engr, 2014), Adam Mellott (Chem Engr, 2014), Saba Ghazvini (Bioengineering, tbd), Shara Thati (Pharm Chem, 2016), Thora Whitmore (Bioengineering 2016)

MS: Vivian Robertson (Pharm Chem, 2013), Mark Bailey (Bioengineering, 2010), Keerthana Devarajan (Bioengineering, 2011)

Student advising (undergraduate researchers)

Pharmacy: Grace Ulrich, Lei Cheung, Abby Petrulis, Hollie Wickam, Kristen Fischer

Chemical Engineering: He Li, Shara Thatti, Connor Bybee, Jason Christian, Hanny Sawaf, Benjamin Johnston, Brian Kim, Francis Pamatmat, Carolynn Stone, Ryan Moulder, Sebastian Bohn, Vignish Raghumraman, John Gerber, Joe Rasmussen, Michael Choi, Eva Mohr (Mechanical), Hannah Leiker, Apexa Shah, Jacob Thompson

Chemistry: Zachary Nicolay, Reese Willis

Summer URP: Grace Ulrich, Yomna Badawi, Shih-Hsuan Huang, Rachel Seo

Highschool: Samantha Farb

Postdoctoral Scientists (includes visiting scientists and research associates)

Shuang Cai, Padmaja Gunda, Yumei Xie, Yepeng Luan, Shaofeng Duan, Sanjeewa Senadheera, Jaden Jungho Jin, Ti Zhang, Chad Groer

Employment of graduates (includes persons employed but have not yet completed all degree requirements):

Adel Alhowyan, MS (lecturer, King Saud University)
Taryn Bagby, PhD (Scientist II, Recro Gainesville)
Shuang Cai, PhD (Principal Scientist, HylaPharm)

Shaofeng Duan, PhD (Full Professor, Henan University, China)
 Padmaja Gunda, PhD (Assistant Professor, Chemistry, Columbia Basin College)
 David Hart, MS (Research & Development Manager, PhytoTechnology Laboratories)
 Jaden Jungho Jin, PhD (Assistant Professor, University of Pittsburg)
 Ryan Moulder, PhD (Research Scientist, Amgen)
 Yepeng Luan, PhD (Instructor, Medicinal Chemistry, Qingdao University, Qingdao, China)
 Abby Petrusis, MS (Pharmacy Resident at U. S. Public Health Service Phoenix Indian Medical Center)
 Sanjeewa Senadheera, PhD (Research Scientist, Lancaster Laboratories / Eurofins)
 Alisha Simonian, MS (Senior Product Development Scientist, Nitto AVECIA Pharma Services)
 Ninad Varkhede, PhD (Senior Scientist, Merck Pharmaceuticals)
 Yumei Xie, PhD (Research Associate, Pacific Northwest National Laboratory)
 Evelyn Yanez, MS (Senior Research Associate, Genentech)
 Qihong Yang, PhD (CMC consultant, Astex Pharmaceuticals)
 Ti Zhang, PhD (Research Scientist, HylaPharm)
 Yunqi Zhao, PhD (Associate Professor, Kunming Medical University, Kunming, China)

Professional Activities

Peer review (Funding Agencies, ad-hoc unless noted otherwise):

American Cancer Society, Drug development study section *ad hoc* reviewer (2012-2014), full member (2014-2019)
 National Institutes of Health (NIH), NCI RC1 2009, NCI R43(SBIR) 2011, NIGMS(MBRS) 2010-2013, NIGMS(SCORE) 2016, NCI SBIR 2014, R15 2014, NCI SBIR 2015, NIH UH2/3 2015, NIH R01/R21 Bioengineering Sciences and Technologies (BST) 2015, NIH R01/R21 Developmental Therapeutics (2017, 2018, 2019), NCI R03/R21 Clinical and Translational Review Panel (2019)
 National Science Centre (NARODOWE CENTRUM NAUKI), Poland, 2013
 United Kingdom Association for International Cancer Research (AICR), 2010
 Canadian National Sciences and Engineering Research Council (NSERC), 2008
 Netherlands Technology Foundation (STW), 2009
 Hong Kong Innovation and Technology Support Programme (ITSP), 2008
 University of Houston Gear Program, 2007

Peer review (Publications):

Ad hoc Editor for issue of Advanced Drug Delivery Reviews (2 issues, 2008 and 2011)
 Ad hoc reviewer for: Advanced Drug Delivery Reviews, Biomacromolecules, Biomaterials, Biomedical Chromatography, Biopharmaceutics & Drug Disposition, Biophysical Chemistry, Clinical Pharmacokinetics, Drug Development and Industrial Pharmacy, European Journal of Pharmaceutics and Biopharmaceutics, International Journal of Pharmaceutics, Journal of Biomaterials Research, Journal of the American Chemical Society, Journal of Biomaterials Science: Polymer Edition, Journal of Biomedical Materials Research Part A, Journal of Chromatography B, Journal of Controlled Release, Journal of Pharmaceutical Sciences, Journal of Pharmacy and Pharmaceutical Sciences, Phytotherapy Research

Member: American Association of Pharmaceutical Scientists (active), American Association for Cancer Research (inactive), American Institute of Chemical Engineers (inactive)

Service

DEPARTMENT

Graduate student admissions committee, Spring 2007-present
 Coordinator for Higuchi Awards to 6th year pharmacy students, Spring 2007-present
 Coordinator for Enz Awards to 6th year pharmacy students, Spring 2007-present
 Graduate student recruiting at Midwest American Chemical Society meeting, October 2009, 2010, 2012
 Presenter in Atlanta NSF-industry meeting for I/UCRC CPMF (Industry/University Cooperative Research Center for Center for Pharmaceutical Manufacturing and Formulation), November 2009
 Graduate student recruiting at Central Arkansas University, November 2008
 Faculty retreat planning committee member, Spring 2007
 Graduate student recruiting at Missouri State University, October 2007

SCHOOL

PharmD admissions committee member, Spring 2010-present
 PharmD and MBA dual degree admissions committee member, Spring 2008-present
 Pharmaceutical Chemistry Chair 5-year review committee, November 2014 – February 2015

UNIVERSITY

University Conflict of Interest Committee, October 2019-present
University Senate Judicial Board, October 2017-present
BioEngineering Center Director Search Committee, June 2018
Animal Care Advisory Council, November 2013 - June 2017
Vice-Chair of Institutional Animal Care and Use Committee (IACUC) (October 2011 – August 2013)
Chair of IACUC protocol development subcommittee, July 2009 – August 2013
IACUC member January 2007-August 2013
Interviewer for University Assessment of General Education, Spring 2007 and 2008
Student recruiter for KU at Annual Biomedical Research Conference for Minority Students (ABRCMS), St. Louis, 2011; Nashville, TN, 2013
Japan Alumni Outreach Seminars, on behalf of KU Endowment Association and Department of Pharmaceutical Chemistry, Tokyo, Japan, May 2017

LOCAL, STATE, REGIONAL

Invited speaker at Kansas City Chapter of American Cancer Society fundraising dinner, August 2009 (unable to attend)
Judge at PSGRM Annual Conference, Kansas City, June 2007
Judge at Annual Biomedical Research Conference for Minority Students (ABRCMS), November 2011, 2013

NATIONAL

Reviewer and ad hoc study section member for American Cancer Society (ACS), Cancer Drug Development panel, 2012-2015
Reviewer and standing study section member for American Cancer Society (ACS), Cancer Drug Development panel, 2015-2018
Reviewer National Institutes of Health (NIH), R01 proposal review: Developmental Therapeutics, ad hoc, 2016-2019
Reviewer National Institutes of Health (NIH), R01/R21 proposal review: Bioengineering Sciences and Technologies (BST) study section, ad hoc, 2015.
Reviewer National Institutes of Health (NIH), NCI proposal review: cancer detection, diagnosis, and treatment technologies for global health (UH phase 2 and 3), ad hoc, 2015
Reviewer National Institutes of Health (NIH), SBIR contract review: cancer stem cell culture systems (Phase 1 and Phase 2), ad hoc, 2015
Reviewer National Institutes of Health (NIH), SBIR contract review: cancer stem cell treatments(Phase 1 and Phase 2), ad hoc, 2014
Reviewer for National Institutes of Health (NIH) R15, ad hoc, 2014
Reviewer for National Institutes of Health (NIH), SBIR contract review panel: anticancer antibodies, ad hoc 2011
Reviewer for National Institutes of Health (NIH), MBRS review panel, ad hoc 2010, 2012
Reviewer for National Institutes of Health (NIH), RC1 grants, ad hoc 2009
Member of Scientific and Medical Advisory Board, Exogenesis Corporation, Billerica, MA, 2009-present
Member and participant in national meetings – American Chemical Society, 2009-present
Member and participant in national meetings – American Association of Pharmaceutical Sciences, 2005-present
Member and participant in national and international meetings, abstract reviewer – Controlled Release Society, 2002-2014
Member and participant in national meetings – American Institute of Chemical Engineers, 2000-2005
Reviewer for Advanced Drug Delivery Reviews, Biomacromolecules, Biomaterials, Biomedical Chromatography, Biopharmaceutics & Drug Disposition, Biophysical Chemistry, Clinical Pharmacokinetics, Drug Development and Industrial Pharmacy, European Journal of Pharmaceutics and Biopharmaceutics, International Journal of Pharmaceutics, Journal of Biomaterials Research, Journal of Biomaterials Science: Polymer Edition, Journal of Biomedical Materials Research Part A, Journal of Chromatography B, Journal of Controlled Release, Journal of Pharmaceutical Sciences, Journal of Pharmacy and Pharmaceutical Sciences, Phytotherapy Research, Nanomaterials
Reviewer for University of Houston Gear Program, ad hoc 2007

INTERNATIONAL

Reviewer for National Science Centre (NARODOWE CENTRUM NAUKI), Poland, ad hoc 2013
Editorial Board member, Journal of Pharmaceutics, 2012-2013
Reviewer for Icelandic Research Fund, ad hoc 2012
Reviewer for Association for International Cancer Research (AICR), United Kingdom; ad hoc 2010
Developed, organized and taught short course (1 full credit hour) “Drug Delivery systems”
Tsukuba University, Tsukuba, Japan (July 2009 and 2010)

Shandong University, Jinan, China (July 2009)
 Reviewer for Hong Kong Innovation and Technology Support Programme (ITSP), ad hoc 2008
 Theme issue editor for Advanced Drug Delivery Reviews, 2 theme issues, 2008 and 2009
 Reviewer for Canadian National Sciences and Engineering Research Council (NSERC), ad hoc 2007
 Reviewer for Netherlands Technology Foundation (STW), ad hoc 2007 and 2008

Grants

Active

1R01CA173292-01 (PI:Forrest) National Institute of Health/National Cancer Institute Title: Biomaterials for treatment of head and neck cancers Role: PI	03/01/13 – 2/28/19 (no cost)	
R01AI1138970 (PI: W.L. Picking) calendar National Institutes of Health Title: <i>Vaccines to counter emerging antibiotic resistance</i> Pursue our hypothesis that Haf-Fusions from <i>Pseudomonas aeruginosa</i> , <i>Salmonella enterica</i> and <i>Shigella</i> spp. will provide serotype-independent protection against all strains of these pathogen including MDR species/strains Role: Co-Investigator	06/01/2018 – 05/31/2023	1.2
BioNEXUS KCALSI Title: Development of cancer vaccines using dogs as a translational model Role PI	12/1/2018-11/30/2019	
IAMI Frontiers (PI: Swerdlow) effort KUMC Title: Pharmacokinetic Analysis of a Novel Bioenergetic Medicine Esters Goal: Synthesis and preliminary PK testing of new bioenergetic prodrugs. Role: co-investigator	05/15/2018 – 06/30/2019	0.1
KUADC (PI: L Forrest) calendar KUMC Title: <i>Bioenergetic prodrugs for treatment of Alzheimer's</i> Goal: To develop a pilot library of bioenergetic drugs Role: PI	07/01/2018 – 06/30/2019	0.24
SBIR Phase 1 (PI: Michaelis) effort Aerobyx LLC/NIH flowthru Title: Targeting Bioenergetic Flux for Alzheimer's Disease Management Goal: Scale up and production of a bioenergetic prodrug, preliminary animal testing Role: co-investigator	09/01/2018 – 03/30/2019	0.1
Industrial Contract (PI: Forrest) HylaPharm LLC Translation development of intralymphatic chemotherapy Role: Principal investigator	05/01/12- 02/28/19	

Recently completed (last 3 years)

National Institutes of Health (NIH) / National Institute for Allergy and Infectious Disease (PI: Cai) 7/1/2017-6/30/2018
Generating synergy between protein and non-protein macromolecular adjuvants
Role: co-investigator

Kansas State University – College of Veterinary Medicine & Veterinary Health Center 6/1/15-12/31/17
Proof-of-concept study locally administering a nanotherapeutic formulation of hyaluronan conjugated cisplatin to dogs with naturally-occurring metastatic apocrine gland anal sac adenocarcinoma
Role: co-investigator

1U01FD005285 (lead PI: Volkin, Co-PI: Forrest) 10/1/14-9/30/17
FDA (Food and Drug Administration)
Title: Development of an Integrated Mathematical Model for Comparative Characterization of Complex Molecules

Industrial Contract (PI: Forrest)
Akari Pharmaceuticals
Formulation of Coversin for subcutaneous sustained release 8/15/2016-1/15/2018
Role: Principal Investigator

National Institutes of Health (NIH) / National Cancer Institute (PI: Groer) 2/1/2017-1/31/2018
SBIR 1R43CA203142-01A1
Aerosolized platinum nanoparticle chemotherapy for lung cancer
Role: co-investigator

National Institutes of Health (NIH) / National Cancer Institute (NCI) 9/10/2015-10/1/2016
Contract Number: HHSN261201500047C (NCI control # N43-CO-2015-0047)
Targeted nanoparticle treatment for breast cancer stem cells
Role: co-investigator/PI subaward

KINBRE: Local immunosuppressive treatment of ulcerative colitis 05/01/2016 – 04/30/2017
NIH P20GM103418 (PI P20: Wright)
Kansas IDeA Network of Biomedical Research Excellence (K-INBRE), Translational Partnership Award
Role: PI (project)

Proof of Concept Award (PI: Forrest) 5/1/2015-6/30/2016
University of Kansas Commercialization and Technology Center
Development of therapy for triple negative breast cancer
Role: PI

Proof of Concept Jay Award (PI: Forrest) 7/1/2015-6/30/2016
Higuchi Biosciences Center
Mechanistic understanding of oxidation of therapeutic proteins after subcutaneous administration
Role: PI

Proof of Concept Award (PI: Rowe) 4/1/2014-6/30/2015
University of Kansas Commercialization and Technology Center
Formulation for enhanced hair growth
Role: Co-PI

1R56AI091996 (PI: Berkland) 08/15/12 – 07/31/15
Targeted nanoscale antigen arrays for treating autoimmune diseases
NIH

EXHIBIT B

EXHIBIT B

<u>Exhibit No.</u>	<u>Description</u>
1001	U.S. Patent No. 8,114,833, <i>Propylene Glycol-Containing Peptide Formulations which are Optimal for production and for Use in Injection Devices</i> (issued Feb. 14, 2012)
1003	Prosecution history excerpts for U.S. Patent No. 8,114,833
1004	International Publication No. WO 03/002136, <i>Stable Formulation of Modified GLP-1</i> (published Jan. 9, 2003) (“Flink”)
1005	International Publication No. WO 2004/004781, <i>Liquid Formulations with High Concentration of Human Growth Hormone (hgh) Comprising 1,2-Propylene Glycol</i> (published Jan. 15, 2004) (“Betz”)
1006	U.S. Patent No. 6,268,343, <i>Derivatives of GLP-1 Analogs</i> (filed Feb. 26, 1999) (issued July 31, 2001)
1007	EP 0 923 950, <i>Liquid Agent for Contact Lens</i> (issued June 23, 1999)
1008	Powell et al., <i>Parenteral Peptide Formulations: Chemical and Physical Properties of Native Luteinizing Hormone-Releasing Hormone (LHRH) and Hydrophobic Analogues in Aqueous Solution</i> , 8(10) PHARMACEUTICAL RESEARCH 1258 (1991)
1009	E. Epperson, <i>Mannitol Crystallization in Plastic Containers</i> , 35 AM. J. HOSP. PHARM. 1337 (1978)
1010	Griffin et al., <i>Polyhydric Alcohols</i> , CRC HANDBOOK OF FOOD ADDITIVES 431 (Thomas E. Furia ed., 2d ed. 1972)
1011	J. Jacobs, <i>Factors Influencing Drug Stability in Intravenous Infusions</i> , 27 J. HOSP. PHARM. 341 (1969)
1012	MODERN PHARMACEUTICS (Gilbert S. Banker et al. eds., 3d ed. 1996)
1013	REMINGTON’S PHARMACEUTICAL SCIENCES (18th ed. 1990)
1014	International Publication No. WO 03/072195, <i>Method for Administering GLP-1 Molecules</i> (published Sept. 4, 2003)
1015	INTENTIONALLY LEFT BLANK
1016	INTENTIONALLY LEFT BLANK

<u>Exhibit No.</u>	<u>Description</u>
1017	U.S. Patent No. 8,759,291, <i>Methods of Treatment using Exendin Peptides or GLP-1 Peptides</i> (filed Apr. 5, 2011) (issued June 24, 2014)
1018	U.S. Patent Application Publication US 2005/0 48497, <i>Method for Administering GLP-1 Molecules</i> (July 7, 2005)
1019	International Publication No. WO 95/22560 A1, <i>Pharmaceutical Formulations of CNTF</i> (published Aug. 24, 1995)
1020	U.S. Patent No. 6,458,924, <i>Derivatives of GLP-1 Analogs</i> (filed Sept. 16, 1999) (issued Oct. 1, 2002)
1021	International Publication No. WO 00/37098 A1, <i>Shelf-Stable Formulation of Glucagon-Like Peptide-1</i> (published June 29, 2000)
1022	Handbook of Pharmaceutical Excipients (3d ed. 2000)
1023	Handbook of Pharmaceutical Excipients (4th ed. 2003)
1024	Akers, <i>Formulation Development of Protein Dosage Forms</i> in DEVELOPMENT AND MANUFACTURE OF PROTEIN PHARMACEUTICALS (2002)
1025	International Patent Publication No. WO 1999/040788, <i>Inotropic and Diuretic Effects of Exendin and GLP-1</i> (published August 19, 1999)
1026	DEVELOPMENT OF BIOPHARMACEUTICAL PARENTERAL DOSAGE FORMS (John A. Bontempo ed., 1997)
1027	Gaitlin, <i>Formulation and Administration Techniques to Minimize Injection Pain and Tissue Damage Associated with Parenteral Products</i> in INJECTABLE DRUG DEVELOPMENT (1999)
1028	A DICTIONARY OF CHEMISTRY (1996) (excerpts)
1029	FDA Guidance for Industry - Chemistry Manufacturing and Controls (2003)
1030	U.S. Patent No. 5,514,097, <i>Self Administered Injection Pen Apparatus and Method</i> (issued May 7, 1996)
1031	International Publication No. WO 93/19175, <i>Receptor for the Glucagon-Like-Peptide-1 (GLP-1)</i> (published Sept. 30, 1993)
1032	International Publication No. WO 99/43705, <i>N-Terminally Truncated GLP-1 Derivatives</i> (published Sept. 2, 1999)

<u>Exhibit No.</u>	<u>Description</u>
1033	International Publication No. WO 99/43706, <i>Derivatives of GLP-1 Analogs</i> (published Sept. 2, 1999)
1034	International Publication No. WO 99/43707, <i>N-Terminally Modified GLP-1 Derivatives</i> (published Sept. 2, 1999)
1035	International Publication No. WO 98/08871, <i>GLP-1 Derivatives</i> (published Mar. 5, 1998)
1036	International Publication No. WO 02/46227, <i>GLP-1 Fusion Proteins</i> (published June 13, 2002)
1037	International Publication No. WO 99/43708, <i>GLP-1 Derivatives of GLP-1 and Exendin with Protracted Profile of Action</i> (published Sep. 2, 1999)
1038	International Publication No. WO 99/43341, <i>GLP-1 Derivatives with Helix-Content Exceeding 25%, Forming Partially Structured Micellar-like Aggregates</i> (published Sept. 2, 1999)
1039	International Publication No. WO 87/06941, <i>Insulinotropic Hormone</i> (published Nov. 19, 1987)
1040	International Publication No. WO 0/11296, <i>Insulinotropic Hormone</i> (published Oct. 4, 1990)
1041	International Publication No. WO 91/11457, <i>GLP-1 Analogs useful for Diabetes Treatment</i> (published Aug. 8, 1991)
1042	International Publication No. WO 98/43658, <i>Glucagon-Like Peptide-1 Analogs</i> (published Oct. 8, 1998)
1043	International Publication No. EP 0 708 179, <i>Glucagon-Like Insulinotropic Peptide Analogs, Compositions, and Methods of Use</i> (published Dec. 22, 2004)
1044	International Publication No. EP 0 699 686, <i>Biologically Active Fragments of Glucagon-Like Insulinotropic Peptide</i> (published Oct. 8, 2003)
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1046	J. Sturis et al., <i>GLP-1 Derivative Liraglutide in Rats with β-cell Deficiencies: Influence of Metabolic State on β-cell Mass Dynamics</i> , 140 BRIT. J. PHARMACOLOGY 123 (2003)

<u>Exhibit No.</u>	<u>Description</u>
1047	J. Fransson et al., <i>Local Tolerance of Subcutaneous Injections</i> , 48 J. PHARM. PHARMACOL. 1012 (1996)1
1048	L. Gerweck et al., <i>Cellular pH Gradient in Tumor Versus Normal Tissue: Potential Exploitation for the Treatment of Cancer</i> , 56 CANCER RESEARCH 1194 (1996)
1049	I. Madshus, <i>Regulation of Intracellular pH in Eukaryotic Cells</i> , 250 BIOCHEM. J. 1 (1988)
1050	C. Fox et al., <i>Ability to Handle, and Patient Preference for, Insulin Delivery Devices in Visually Impaired Patients with Type 2 Diabetes</i> , 19(4) PRACTICAL DIABETES INT 104 (2002)
1051	A.M. Robinson et al., <i>Subcutaneous Versus Intravenous Administration of Heparin in the Treatment of Deep Vein Thrombosis; Which do Patients Prefer? A Randomized Cross-Over Study</i> , 69 POSTGRAD MED J. 115 (1993)
1052	D. Schade et al., <i>The Intravenous, Intraperitoneal, and Subcutaneous Routes of Insulin Delivery in Diabetic Man</i> , 28 DIABETES 1069 (1979)
1053	X.H. Zhou et al., <i>Peptide and Protein Drugs: I. Therapeutic Applications, Absorption and Parenteral Administration</i> , 75 INT'L J. PHARM. 97 (1991)
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1055	C.M.B. Edwards et al., <i>Peptides as Drugs</i> , 92 Q J MED 1 (1999)
1056	C. Akiyama et al., <i>Comparison of Behavior in Muscle Fiber Regeneration After Bupivacaine Hydrochloride- and Acid Anhydride-Induced Myonecrosis</i> , 83 ACTA NEUROPATHOL 584 (1992)
1057	Alfred Martin, PHYSICAL PHARMACY (4th ed. 1993)
1058	S. Borchert et al., <i>Particulate Matter in Parenteral Products: A Review</i> , 40 J. PARENTERAL SCI. & TECH. 212 (1986)
1059	X. Chang et al., <i>NMR Studies of the Aggregation of Glucagon-Like Peptide-1: Formation of a Symmetric Helical Dimer</i> , 515 FEBS LETTERS 165 (2002)
1060	M. Stranz et al., <i>A Review of pH and Osmolarity</i> , 6(3) INT'L J. PHARM. COMPOUNDING 216 (2002)

<u>Exhibit No.</u>	<u>Description</u>
1061	PHARMACEUTICS THE SCIENCE OF DOSAGE FORM DESIGN (Michael E. Aulton ed., 2d ed. 2002)
1062	D. Dubost et al., <i>Characterization of a Solid State Reaction Product from a Lyophilized Formulation of a Cyclic Heptapeptide. A Novel Example of an Excipient-Induced Oxidation</i> , 13(12) PHARM. RESEARCH 1811 (1996)
1063	U.S. Patent No. 4,425,346, <i>Pharmaceutical Compositions</i> (issued Jan 10, 1984)
1064	U.S. Patent No. 6,207,684, <i>Compounds with Combined Antihistaminic and Mast Cell Stabilizing Activities, Intended for Ophthalmic Use</i> (issued Mar. 27, 2001)
1065	U.S. Patent No. 6,440,460, <i>Pharmaceutical Compositions Containing Buffered Ortho Ester Polymers</i> (issued Aug. 2, 2002)
1066	J. Bothe et al., <i>Peptide Oligomerization Memory Effects and Their Impact on the Physical Stability of the LP-1 Agonist Liraglutide</i> , 16 MOL. PHARMACEUTICS 2153 (2019)
1067	M.J. Akers, <i>Excipient-Drug Interactions in Parenteral Formulations</i> , J PHARM SCI 91(11) (2002)
1068	U.S. PHARMACOPEIA XXII, NATIONAL FORMULARY XVII (1990)
1069	R. Noel, <i>Statistical Quality Control in the Manufacture of Pharmaceuticals</i> , 4(4) QUALITY ENGINEERING 649 (1992)
1070	NOTE FOR GUIDANCE SPECIFICATIONS: TEST PROCEDURES AND ACCEPTANCE CRITERIA FOR NEW DRUG SUBSTANCES AND NEW DRUG PRODUCTS: CHEMICAL SUBSTANCES (CPMP/ICH/367/96) (2000)
1071	M. Gnanalingham et al., <i>Accuracy and Reproducibility of Low Dose Insulin Administration Using Pen-Injectors and Syringes</i> , 79 ARCH. DIS. CHILD 59 (1998)
1072	C. Burke et al., <i>The Adsorption of Proteins to Pharmaceutical Container Surfaces</i> , 86 INT'L J. OF PHARMACEUTICS 89 (1992)
1073	T. Asakura et al., <i>Occurrence of Coring in Insulin Vials and Possibility of Rubber Piece Contamination by Self-Injection</i> , 121(6) YAKUGAKU ZASSHI 459 (2001)

<u>Exhibit No.</u>	<u>Description</u>
1074	M. Roe et al., <i>Dose Accuracy Testing of the Humalog® Humulin® Insulin Pen Device</i> , 3(4) DIABETES TECH. & THERAPEUTICS 623 (2001)
1075	Parenteral Drug Association, <i>Points to Consider for Cleaning Validation. Technical Report No. 29</i> , 52(6 suppl) PDA J PHARM SCI TECHNOL. 1 (1998)
1076	WIPO Patentscope PCT Bibliography Data for PCT/DK2004/000792